

Response of the Cardiovascular System to Vibration and Combined Stresses

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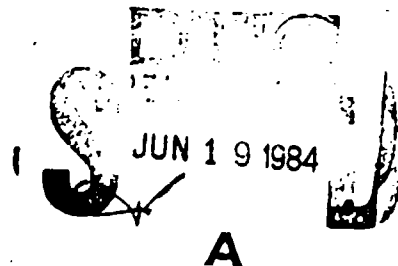
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that were counterproductive (phase lag) to the maintenance of AP. This noninvasive technique may indirectly predict the characteristics of vascular resistance in people and, therefore, may delineate changes in the vasculature as a result of disease or interventions such as weightlessness or endurance training.

II. Eight chronically instrumented dogs with A-V nodal blockade and a heart rate which was computer controlled in either an open or closed-loop manner were used to investigate three specific topics:

A. IS THE NEURAL FEEDBACK CONTROL OF HEART RATE OPERATING TO PRODUCE OPTIMAL CARDIOVASCULAR REGULATION DURING TIME-DEPENDENT ACCELERATION STRESS? Each dog's ability to regulate AP while exposed to $\pm 2G_z$ sinusoidal acceleration from 0.005 to 0.23 Hz was measured using first the dog's closed-loop HR control and next HR bionically controlled by AP. We found that oscillations in AP can be reduced $\sim 1/2$ at all frequencies with bionic rather than natural control of HR.

B. THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN THE MAINTENANCE OF STEADY STATE CARDIOVASCULAR REGULATION IN RESPONSE TO CHANGES IN HEART RATE. The cardiovascular effects of 7 randomly applied step changes in HR from 40 to 220 b/min were explored before and after ganglionic blockade. We found that: 1) step increases in HR from 60 to 180 b/min in unblocked dogs produced large slow (period ~ 30 sec) oscillations in AP due to neurally mediated peripheral vascular oscillations superimposed on a doubled cardiac output. 2) The contributions of autonomic effector activity were significant for all variables at some HRs and for some variables at all HRs.

C. STEADY STATE CARDIOVASCULAR RESPONSES TO COMBINATIONS OF INCREASED HEART RATE AND INCREASED $+G_z$ ACCELERATION. Steady state responses to step changes in HR were determined in the same dogs at $0G_z$, $+1G_z$ and $+2G_z$. We found that: 1) The combined effect of increasing HR and increasing $+G_z$ resulted in an 86% decrease in SV at $+2G_z$ for HR's of 220 b/min compared to SV at $0G_z$ and 40 b/min. 2) Steady state levels of mean AP were the same at 0, $+1$ and $+2G_z$ acceleration levels. The maintenance of AP at $+2G_z$ was due to an 83% increase in resistance to counteract the loss of venous return.

III. CARDIOVASCULAR RESPONSES OF UNTRAINED AND ENDURANCE TRAINED DOGS TO OSCILLATORY BLOOD VOLUME SHIFTS. The ability of normal and endurance trained dogs to maintain AP while undergoing $\pm 2G_z$ sinusoidal acceleration from 0.008 to 0.23 Hz were compared. Fourier analysis indicated that while both groups experienced comparable blood volume shifts and maintained comparable levels of AP, the vasculature of trained dogs was more sluggish, (greater phase lag). As a result, trained dogs had larger HR responses than did untrained dogs.

IV. CHANGES IN PEAK LEFT VENTRICULAR WALL STRESS IN NORMAL AND CARDIAC DENERVATED CANINES DURING SINUSOIDAL ACCELERATION A comparison of changes in peak left ventricular wall stress in normal and cardiac denervated dogs during $\pm 2G_z$ sinusoidal acceleration from 0.005 to 0.23 Hz was made to determine the effects of extrinsic cardiac innervation on wall stress. Left ventricular pressure, major and minor axes and wall thickness were used to calculate peak wall stresses employing a prolate ellipsoid computer model. The largest acceleration-induced peak wall stresses for 6 normal and 6 denervated dogs occurred at 0.025 Hz. Wall stresses for the normal dogs were lower than for the cardiac denervated dogs below 0.02 Hz.

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Benjamin S. Kelley, Ph. D.**

**Wenner-Gren Research Laboratory
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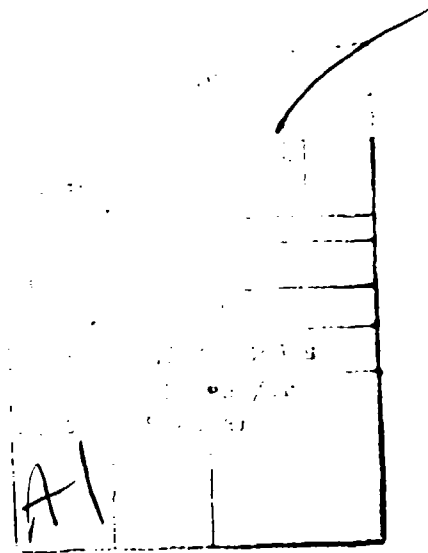
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PREFACE

In this final report, the following four projects are summarized:

- I. Heart Rate Responses of Humans to Sinusoidally Varying ± 1 G_z Gravitational Stress.
- II. The exploration of a new chronically instrumented animal preparation in which heart rate (via AV sequential pacing) can be computer controlled in either an open or closed-looped manner. The specific topics investigated are:
 - A. Is the Neural Feedback Control of Heart Rate Operating to Produce Optimal Cardiovascular Regulation During Time-Dependent Acceleration Stress?
 - B. The Role of the Autonomic Nervous System in the Maintenance of Steady State Cardiovascular Regulation In Response to Changes in Heart Rate.
 - C. Steady State Cardiovascular Responses to Combinations of Increased Heart Rate and Increased +G_z Acceleration.
- III. Cardiovascular Responses of Untrained and Endurance Trained Dogs to Oscillatory Blood Volume Shifts (Ph.D. Dissertation of Dr. John Charles).
- IV. Changes in Peak Left Ventricular Wall Stress in Normal and Cardiac Denervated Canines During Sinusoidal Acceleration (Ph.D. Dissertation of Dr. Benjamin Kelley).

Projects III and IV have been completed and Projects I and II were in the preliminary development stage at the time funding was terminated.



RESEARCH TEAM

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Instrumentation Specialist:	R. Stanifer
System Analyst:	C. Fischer
Data Analysts:	E. Cremers, G. Hirsch, K. Kelley P. Thudium, M. McMinn, E. Welch and T. Mattingly

The formation of this research team is based on a general plan which integrates the advanced analytical techniques and instrumentation development capabilities of an interdisciplinary team, consisting of physiologists and biomedical engineers, in an effort to resolve problems associated with acceleration stress. Measurements from the invasive instrumentation of the chronically implanted animal preparation of previous and present studies done in our laboratory have been shown in the present study to indicate the most meaningful

variables for assessing acceleration-induced cardiovascular responses with the less invasive measurements available for man. This basic research effort has the potential for providing background information which will lead to improved protective equipment and operational procedures for military personnel exposed to acceleration environments resulting from the optimal utilization of advanced aerospace systems.

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I. HEART RATE RESPONSES OF HUMANS TO SINUSOIDALLY VARYING $\pm 1G_z$ GRAVITATIONAL STRESS

INTRODUCTION

We are engaged in a long term, systematic investigation of the frequency response characteristics of cardiovascular regulation during times of rapid G-onset and/or G blends similar to those associated with ACM's of the AFTI/F-16 aircraft. One of the objectives of our Centrifuge/Cardiovascular Program is based on the premise that the design of effective countermeasures to rapid onset rates of acceleration stress and/or G blends depends upon the understanding of the nature and time constants of individual mechanisms responsible for integrated cardiovascular regulation. This point becomes especially important when combined with the possibility of pre-planned, computer controlled, AFTI flights at low altitude and high speeds. Under these anticipatory G loadings, for example, the design of new anticipatory countermeasures could be greatly aided by our deliberate and organized approach to system identification of cardiovascular G-tolerance mechanisms (1,2,3). It is also our belief that this current basic research effort which uses animals, and more recently human subjects, will provide the background for the implementation of improved training, screening, and operational procedures for young and aging Air Force flight personnel exposed to the acceleration environments of advanced aerospace systems. This is especially needed in relation to potential acceleration-induced cardiovascular embarrassments of flight personnel resulting from pathological and/or aging changes in a particular physiological subsystem.

For example, the need to develop meaningful procedures for the screening of experienced aging flight personnel is of extreme importance in view of the current (and anticipated) acceleration-induced demands made of their cardiovascular systems. It is with this need in mind that we have extended our investigation of the frequency response characteristics of cardiovascular regulation to also include human responses.

The human study described below utilized a slowly rotating platform (Figure 1a) to produce a sinusoidally varying gravitational force and noninvasive instrumentation to measure heart rate and blood pressure when possible. Although relatively simple, the experiment was based on the results from several years of study using chronically instrumented dogs and offers the possibility of classifying the speed with which a particular human cardiovascular system can respond to transient acceleration loadings.

The rationale for the human study was based on one of our earlier studies that revealed a resonant peak in the amplitude of gravitationally-induced heart rate excursions (DEL HR) at 0.015 Hz in all 3 of the human subjects tested (Figure 1b). This observation is noteworthy in that previous work by Gillingham et al (4), investigating eye-level arterial blood pressure (AP) in 3 human subjects during simulated aerial combat maneuvers (SACM), showed a resonant peak in the amplitude of the AP excursions (DEL AP) at about 0.06 Hz. In our dog studies however, both maximal DEL HR and DEL AP in response to $\pm 2 G_z$ sinusoidal acceleration, occurred in the same acceleration frequency range, 0.03 - 0.05 Hz (1,2,3). The apparent differences between the two human studies was probably due to the fact that a very limited number of subjects were

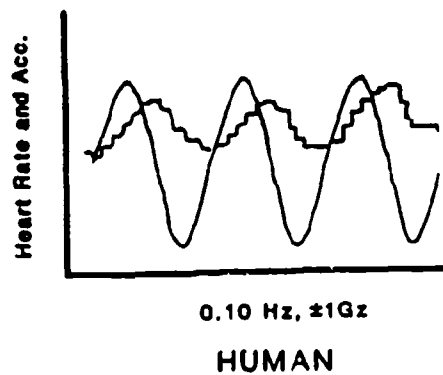
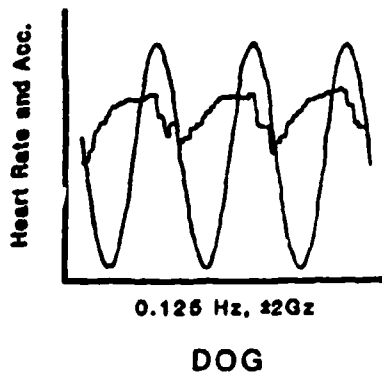
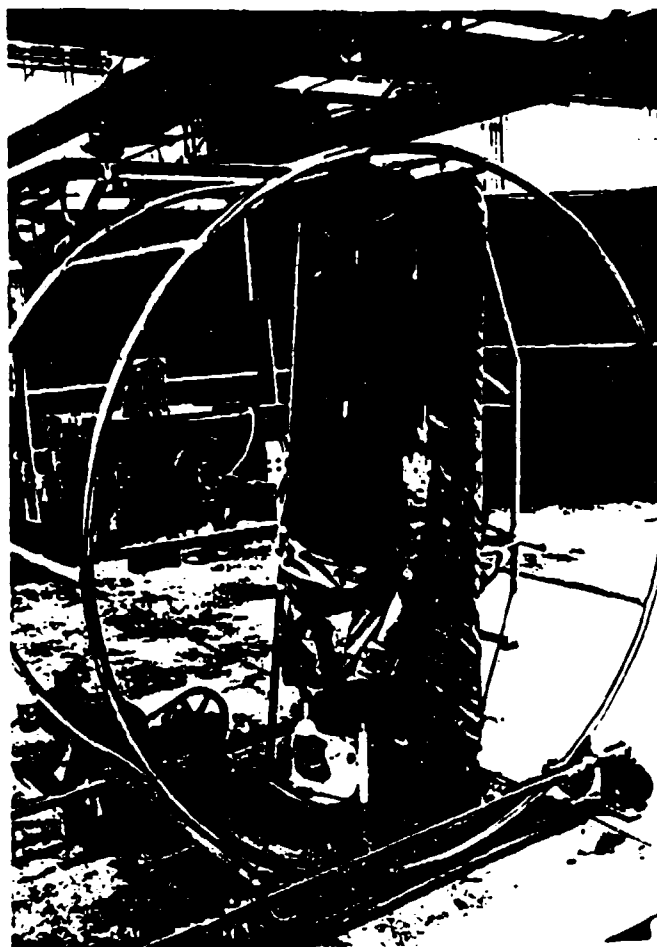


Figure 1a. Modified Circle Electric Bed for producing sinusoidal $\pm 1G$ acceleration. (Dog response is from a centrifuge study.)

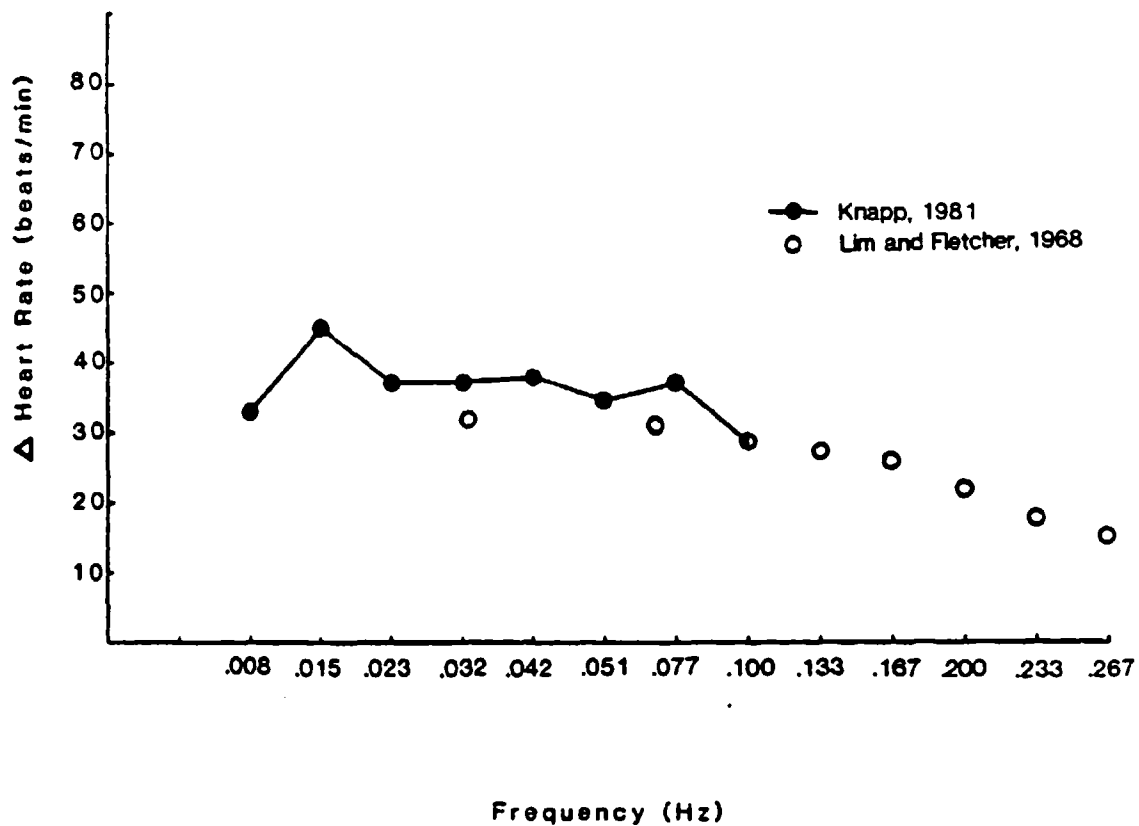


Figure 1b. Amplitude of Human Heart Rate oscillations vs rotation frequency ($\pm 1G$). (Knapp, 81--3 subjects, Lim and Fletcher, 68--7 subjects.)

used in each study and that simultaneous aortic pressure and heart rate were not measured in the same subjects. It was also possible that the peaks in DEL AP and DEL HR for the human responses might have been a result of the different techniques used to produce the responses and/or the value of the G levels (i.e. rotation of the spinal axis in a plane parallel to earth gravity for our preliminary study and +1 to +4 G_z at approximately 30 sec intervals for the SACM for the Gillingham study, data Fourier analyzed). If, however, a separation between maximal DEL HR and DEL AP in humans could be verified, where none exists in dogs, it would help to facilitate a better understanding of the difference in regulation between the two species. In addition, and most importantly, the present study was able to identify the resonant frequency for HR in humans; data which does not currently exist. Further, this identification predicts a technique for classification of the state of cardiovascular regulatory mechanisms as well.

METHODS

The technique used to produce sinusoidally varying $\pm 1 G_z$ gravitational stress was based on our earlier preliminary study which was approved by the University of Kentucky Human Investigation Committee.

The oscillatory acceleration (gravitational) stress was produced by a slow 360 degree rotation of a modified clinical "Circle Electric Bed", at rotational frequencies ranging from 0.007 to 0.10 Hz (i.e., blood to the head, blood to the feet every two minutes and twenty three seconds at the lowest frequency, and 10

seconds at the highest frequency, see Figure 1a). The 360 degree rotation produced a sinusoidally varying ± 1 G stress along the long axis of the cardiovascular system which resulted in oscillatory blood volume shifts. It was expected that the subjects would respond with oscillations in HR and blood pressure with various amplitudes and time relationships to the input sinusoidally varying g-loadings.

Subject Selection and Experimental Protocol:

Subjects were 10 unpaid male volunteers between the ages of 18 and 24. Subjects were required to fill out medical history questionnaires and were excluded on the basis of any cardiovascular problems, history of motion sickness, acute illness of any kind, or any musculoskeletal problems. All subjects were carefully screened, and given information about the experimental procedures. After signing the informed consent form, the subjects were given a familiarization session involving a trial rotation period on the experimental apparatus. The "Circle Electric Bed" was modified to include a special restraint system which allowed subjects to be safely secured for the full 360 degree rotation. The restraints included straps crossing the chest, straps holding the thighs, calves, ankles, and wrists and shoulders of the subjects, and a protective helmet.

Each experiment lasted approximately 45 minutes. First, electrocardiographic leads were attached to the subject, who was initially in a supine position on the platform. The subject was then secured, and allowed to rest for a 10 minute control period. At the end of the control period, blood pressure readings were taken. The subject was then rotated at eight different frequencies for approximately three minutes each. The frequencies

were 0.007, 0.016, 0.024, 0.032, 0.042, 0.053, 0.076, and 0.10 Hz (the periods associated with these frequencies range from 2 min, 23 sec to 10 sec). During the rotation period, HR was continuously monitored. The subject was then allowed a fifteen minute recovery period, and blood pressure monitored once again. The subject was then allowed to leave. A medical monitor was available at all times during the experiment.

RESULTS

The grouped heart rate responses of 10 human subjects to $\pm 1 G_z$ sinusoidal acceleration (gravitational) stress at frequencies from 0.007 to 0.10 Hz are shown in Figure 2a and b, open squares.

The HR data were Fourier analyzed and are presented as the peak-to-peak amplitude of the first harmonic of the HR oscillations/G (Figure 2a) and the corresponding phase angle of the first harmonic with respect to the sinusoidal $\pm 1 G_z$ stress. (Figure 2b). The amplitude of the second harmonic (data not shown) were all less than 15% of the first harmonic and showed no trends with the frequency of the oscillating stress.

Data from 7 tranquilized dogs exposed to $\pm 2 G_z$ sinusoidal acceleration are also plotted on the same graphs for comparison, Figure 2a and b, closed circles. The animal data were analyzed in the same manner as that for the human data but in this case the amplitudes of HR oscillations were divided by two to give the amplitude per G since the animals were undergoing a 2G rather than a 1G stress. For the human subjects, the amplitude of the HR oscillations was 26 ± 9 b/min at 0.007 Hz and increased with increasing acceleration

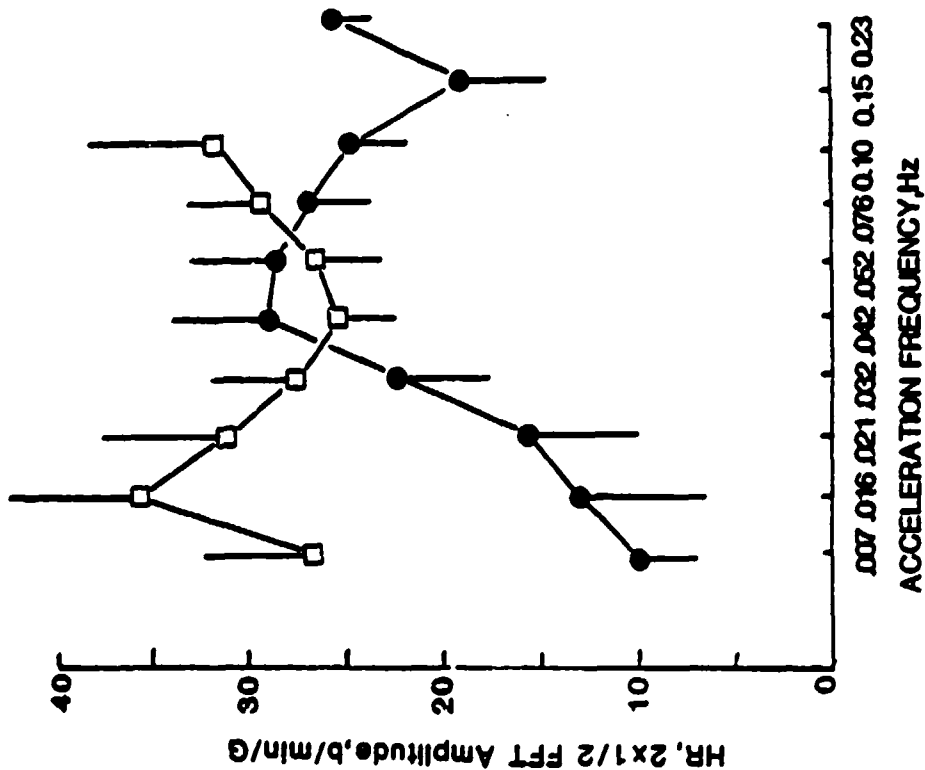


Figure 2a. First harmonic amplitudes of oscillations in heart rate as a function of acceleration frequency for 10 awake human males undergoing $\pm 1 G_z$ and 7 tranquilized dogs undergoing $\pm 2 G_z$.

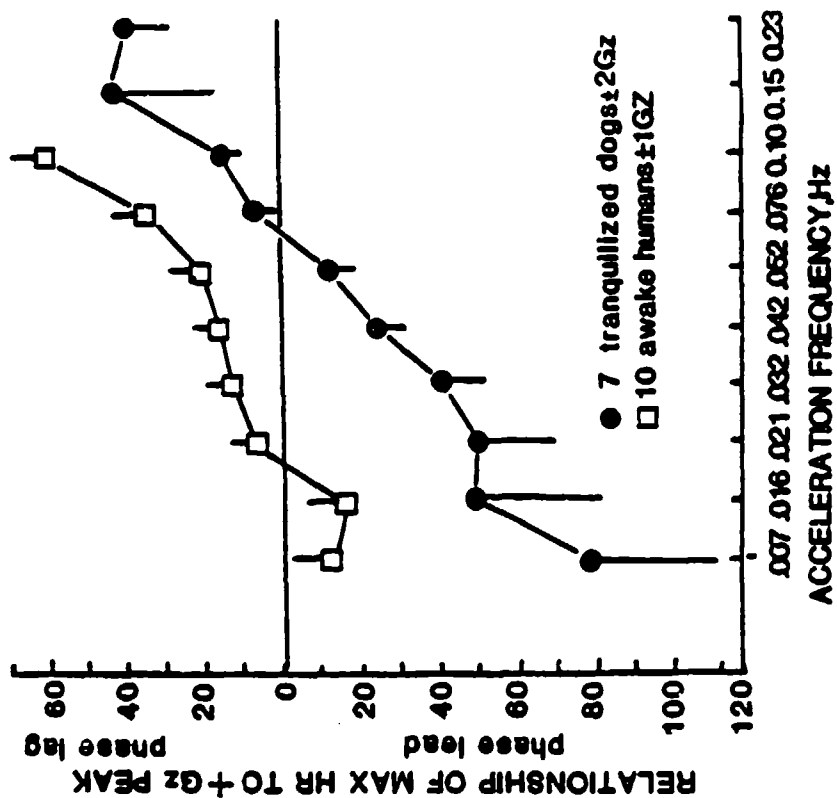


Figure 2b. Phase relationship between acceleration and the first harmonic of heart rate oscillations for 10 awake human males undergoing $\pm 1 G_z$ and 7 tranquilized dogs undergoing $\pm 2 G_z$.

(rotation) frequency, reaching a peak of 36 ± 10 b/min at 0.016 Hz. For frequencies between 0.016 and 0.042 Hz, the excursion in HR decreased with increasing frequency. For frequencies greater than 0.042 Hz, the excursions began again to increase with increasing frequency.

At the two lowest frequencies, Figure 2b, the peak in HR occurred prior to the peak in $+1G_z$ (i.e. phase lead). As acceleration frequency increased, peak HR began to lag peak $+1 G_z$ and became increasingly out of phase with increasing frequency.

The HR responses of the dogs were similar to those of human except that: 1) the largest excursion in heart rate occurred at a higher frequency (i.e., 0.042 Hz for the dogs as compared to 0.016 Hz for humans and 2) the cross over from phase lead to phase lag also occurred at a higher frequency, i.e., between 0.052 and 0.076 Hz for the dogs and 0.016 and 0.021 Hz for humans. The coincidence of the crossover from HR phase lead to lag with the maximum amplitude of the oscillation in both dog and human subjects led us to consider the possibility that these were the same phenomenon occurring at different frequencies in different species. To further examine the similarities between the human and dog HR responses to these acceleration frequencies, the amplitude (Figure 3a) and phase data (Figure 3b) were divided by the resonant frequency i.e., the frequency at which the maximum HR amplitude occurred (0.016 Hz in humans and 0.042 Hz in dogs). The similarities between dog and human responses are now more clearly seen in the graphs of Figure 3a and b. Both species show approximately the same decreased response on either side of their resonant frequency. A secondary increase in HR amplitude for frequencies between two and one-half and five times the resonant

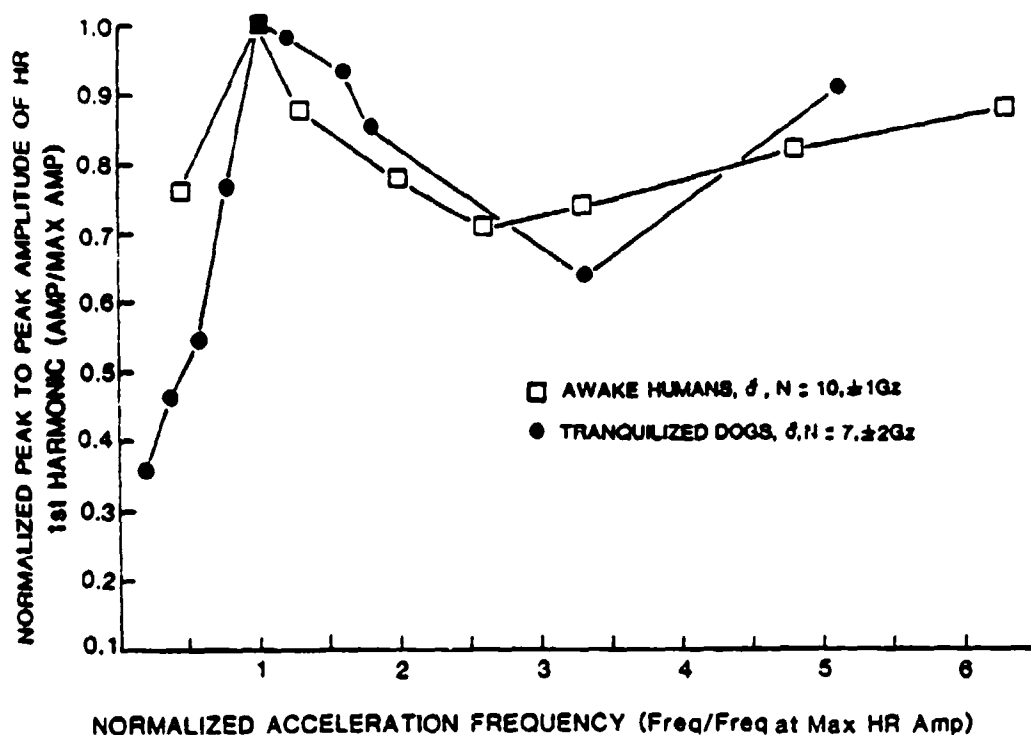


Figure 3a. The ratio of first harmonic amplitude of heart rate oscillations to the maximum amplitude of oscillation (normalized amplitude) plotted against the ratio of frequency of oscillation to the frequency at which the maximum amplitude of oscillation occurred (normalized frequency).

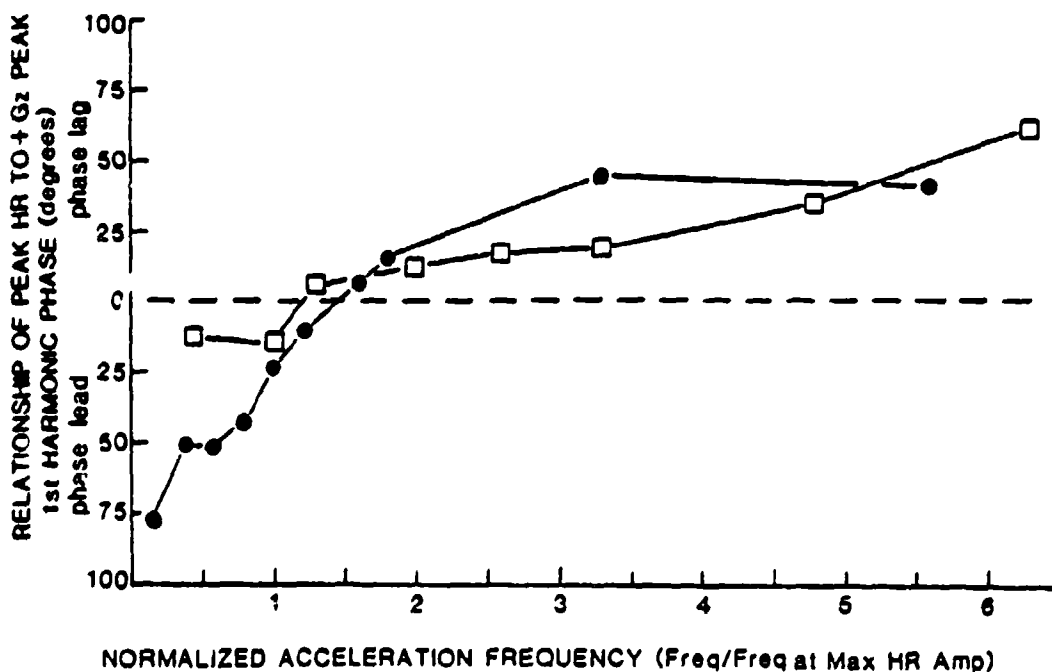


Figure 3b. The phase relationship of the normalized amplitude of heart rate oscillations shown above plotted against the normalized frequency.

frequency is also evident.

In Figure 3b, peak HR responses led the normalized acceleration frequency for values just beyond those at which maximum heart rate oscillations occurred (somewhere between 1.3 and 1.6 times the resonant frequency) for both humans and dogs and, thereafter, increasingly lagged the acceleration cycle.

DISCUSSION

Absolute identification of the human regulatory mechanisms that may be involved with the heart rate responses measured in this study can not be made because of the lack of other variables, such as time-varying blood pressure and total peripheral resistance; both of which would require invasive instrumentation. However, because the overall functional relationship between heart rate and frequency was similar between human and animal, some speculation can be made concerning the regulatory mechanisms of humans by reviewing the matrix of variables that have been obtained from the invasive instrumentation published in previous animal studies (1,2,3).

In those studies, the largest heart rate excursion and the switch from phase lead to lag in dogs were both associated with the acceleration frequency at which total peripheral vascular resistance was lagging the $+G_z$ acceleration peak by 130° to 180° and stroke volume was also lagging by 180° . This situation is an apparent counterproductive one for the regulation of blood. However, the apparent counterproductive response of resistance and stroke volume to the acceleration-induced blood pooling at these particular frequencies was modified by the heart rate response which served to increase

cardiac output during $+2 G_z$ and to decrease it during $-2 G_z$. Chronotropic mechanisms appeared to furnish the only "appropriate" response at this portion of the frequency range.

At frequencies up to 2 times the resonant frequency, stroke volume lagged acceleration by 180° , finally getting in phase by 6 times the resonant frequency (2,3). Further analysis of the response in the same animals, but done following autonomic effector blockade, determined that the stroke volume response was purely hydraulic and the "getting in phase" that occurred with increasing frequency actually reflected passive biomechanical (non-neural) aspects of the circulation, i.e. the time required for blood shifts from upper to lower body compartments to occur. In contrast, the same analysis revealed that the resistance response was of neural origin. At frequencies of less than one fourth the resonant frequency, peripheral resistance amplitudes were large and in phase with acceleration, furnishing effective blood pressure regulation. From one-fourth the resonant frequency up to the resonant frequency, the amplitude of oscillations in resistance were still large but were becoming progressively out of phase with acceleration, approaching 180° at the resonant frequency. For frequencies above the resonant frequency, the phase relationship did not change further, however the amplitude of oscillations diminished rapidly, returning to the hydraulic (non-neural) level by 3 times the resonant frequency.

Prediction of the individual regulatory components of the human cardiovascular response to low frequency $\pm 1 G_z$ sinusoidal acceleration is presented below based on a direct extrapolation from the dog studies and justified on the basis of the striking similarities between the heart rate amplitude and phase "signatures" shown in

Figure 3a and b. The average resonant heart rate response in 10 normal male subjects occurred at 0.016 Hz, a period of ~63 sec, and indicates an average resonance in aortic pressure at the same frequency. The resonance in pressure at this frequency can be ascribed to a stroke volume response that is hydraulic (non-neural in nature) and is 180° out of phase with acceleration and a peripheral vascular resistance response that is neurally mediated and is approaching 180° phase lag. Looking at each of these variables across a frequency range from one-fourth to 6 times the resonant frequency, we predict that the human stroke volume will be 180° out of phase with acceleration for frequencies with periods below 30 sec. For higher frequencies the phase lag decreases until at 6 times the resonant frequency (~10 sec period) the phase lag disappears. Resistance on the other hand has its maximum amplitude of oscillation, as well as maximum effectiveness in terms of phase angle, for frequencies with periods below four minutes. For frequencies with periods ranging from four minutes up to 20 seconds, the amplitude of oscillations decrease to the non acceleration level while getting rapidly out of phase and therefore, contributing greatly to the resonance response seen at 0.016 Hz (period of ~63 sec).

The principal value of this type of systematic, whole body, sinusoidal, low frequency, acceleration stress lies in the interpretation of the heart rate signature to enable the investigator to predict the neurally mediated peripheral vascular time constant for a given human subject. For example, in the Gillingham study (4) the aortic pressure resonance response averaged over only three subjects (Air Force centrifuge volunteers) occurred at ~0.06 Hz (period ~16

sec) as compared to the .016 Hz (period ~63 sec) resonance seen for the 10 subjects (general population) used in the present study. It is interesting to note that in the present study, two of 10 subjects had a resonance (as indicated by both amplitude of oscillation and crossover from phase lead to phase lag) at 0.076 Hz (period ~13 sec) one at .032 Hz (period ~30 sec) two at 0.026 Hz (period ~39 sec) three at 0.016 Hz (period ~63 sec) and two appeared to be approaching resonance at some frequency below 0.007 (period >2 min, 23 sec). Further, those subjects whose heart rate response led the acceleration to higher frequencies had smaller amplitudes of oscillation than did those whose heart rate crossed from phase lead to phase lag at the low frequencies (average amplitude of oscillation of 16 b/min as compared to 39 b/min). These individual variations offer a unique opportunity to test for peripheral vascular differences between subjects. Even more exciting is the potential of this technique to detect peripheral vascular changes in the same subjects as a result of experimental interventions such as endurance training or cardiovascular deconditioning or as a result of the onset of disease states like diabetes.

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II A. IS THE NEURAL FEEDBACK CONTROL OF HEART RATE OPERATING TO PRODUCE OPTIMAL CARDIOVASCULAR REGULATION DURING TIME-DEPENDENT ACCELERATION STRESS?

INTRODUCTION

The rationale for our overall program is based on the premise that the design of effective countermeasures to rapid onset rates of acceleration stress depends upon understanding of the mechanisms responsible for cardiovascular regulation and their frequency response characteristics. This understanding becomes especially important when combined with the possibility of pre-planned computer controlled flights at low altitude and high speeds. The need now exists more than ever before for a very deliberate and organized approach to system identification of physiological mechanisms as to their frequency response characteristics and as to the upper limit of a particular subsystem to function in extreme acceleration environments. For example, from our previous studies, it was not clear that the decreased effectiveness of the dog's cardiovascular regulation in the acceleration frequency range of 0.012 to 0.052 Hz was a true limitation of individual organs (cardiac or vascular). The possibility exists, for example, that the decreased effectiveness of regulation during an unfamiliar acceleration stress may be a result of a less than optimal carotid sinus-heart rate feedback pathway; one that has adapted to the relatively low level, pressure disturbances resulting from normal daily gravitational stimuli and one that has not "seen" relatively high frequency (0.012 - 0.052 Hz) content in pressure disturbances because of the hydraulic filtering provided by the passive circulatory system (previous progress reports). To be more specific, we have

observed that the stroke volume response to +2 G_z acceleration in unblocked dogs dropped to the same values as blocked responses. One explanation of this phenomenon could be that heart rate in the unblocked state climbed to such high values that ventricular filling was substantially compromised during a time when venous return was reduced. Preliminary results from our studies indicate that with the administration of a beta blocker, which reduced peak heart rates during +2 G_z, the diminished stroke volume during +2 G_z was not as pronounced as that occurring in the unblocked state. Beta blockade has also been shown to improve orthostatic tolerance to +3 G_z acceleration stress in humans (1). Observations of this kind suggest that the full capability of cardiovascular regulation, to name just one physiological system, is not known. Understanding and quantification of the upper limits of the regulatory system through basic research with animals can provide the background data base to aid in the design of new countermeasures to acceleration stress. Therefore, in order to determine the potential limits of cardiovascular regulation under G stress, we have begun a preliminary study that will be the basis for a systematic investigation of suspected weaknesses in the acceleration-induced regulatory process.

METHODS

Animal Model:

The animal model was one in which the atrio-ventricular node was destroyed using the technique of Steiner and Kovalik (2) at the time of instrumentation implant surgery. Bipolar atrial and ventricular pacing leads were then added to our standard instruments for measuring aortic flow and right and left ventricular and aortic pressure. This model allows investigator control of heart rate over the range of 30

to 300 b/min. In these animals a ventricular pacemaker (Medtronic) with a screw-in epicardial lead on the apex of the right ventricle was also implanted to pace their hearts at 90 b/min during the three week post operative recovery period.

Pacing Procedures:

At the time of study this lead was disconnected from the pulse generator and used as one half of a bipolar ventricular lead (the other was a Davis and Geck cardiac conduction wire that had been placed at implant surgery less than 1 cm away on the right ventricular epicardial surface. In addition, atrial bipolar leads had been implanted so that at the time of the experiment, atrio ventricular pacing with any desired delay could be delivered. A microprocessor (280 based with 4 D/A and 4 A/D converters) delivered the pacing signal(s) and processed the electromagnetic flow signal to remove the pacing artifacts, integrate the flow over the beat, and report a 2 msec delayed, digital-to-analog, artifact-free, flow signal and a one-beat-delayed value of cardiac output. On initiation of either atrial or ventricular pacing signals (each of 8 msec pulse duration), the flow signal was not read for 22 msec. Atrial ventricular delay was adjustable from 24 msec up to, but not including, the shortest interbeat interval. Both atrial and ventricular pacing signals had independent adjustable gains for voltages between 0 and 8 volts. Paced heart rate as a function of time can be set for any desired waveform (sinusoidal, step, ramp, etc.) or programmed to match the rate response of the intact dog providing that it does not exceed 4000 beats before repeating.

RESULTS

In the present study, for which preliminary results are shown here, each animal's heart was paced in two separate modes during identical acceleration tests (Figure A1). In the first mode, the natural atrial depolarization (driven by the integrated autonomic efferent output arriving at the SA node, dashed lines) was used to trigger ventricular depolarization after a given delay. Preliminary studies indicated that 70 to 100 MS delay (depending on heart rate) produced an optimal ejected volume, but this delay was adjusted for each dog and a range of heart rates. After the animal was tested across our acceleration frequency range with heart rate controlled in this natural manner, control of heart rate in the other mode was established. The input for this mode was aortic arch pressure (solid line) as sensed by the Millar catheter tip transducer. A given diastolic aortic pressure was chosen to trigger first atrial and, after a given delay, then ventricular depolarization. In the right half of Figure A1, the response of aortic pressure to $\pm 2 G_z$ acceleration at .055 Hz is shown at the top for ventricular depolarization triggered by the natural atrial depolarization and at the bottom for the simple atrial/ventricular depolarization triggered by aortic pressure itself. The advantage of the bionic control of heart rate in this dog is apparent with respect to regulation of aortic pressure during $\pm 2 G_z$ sinusoidal acceleration.

A more detailed response from another animal at a lower (.035 Hz) frequency is shown in Figure A2. In the preacceleration control, the intrinsically low heart rate was the result of natural atrial depolarization (70 msec A/V delay) and a sinus arrhythmia accompanied

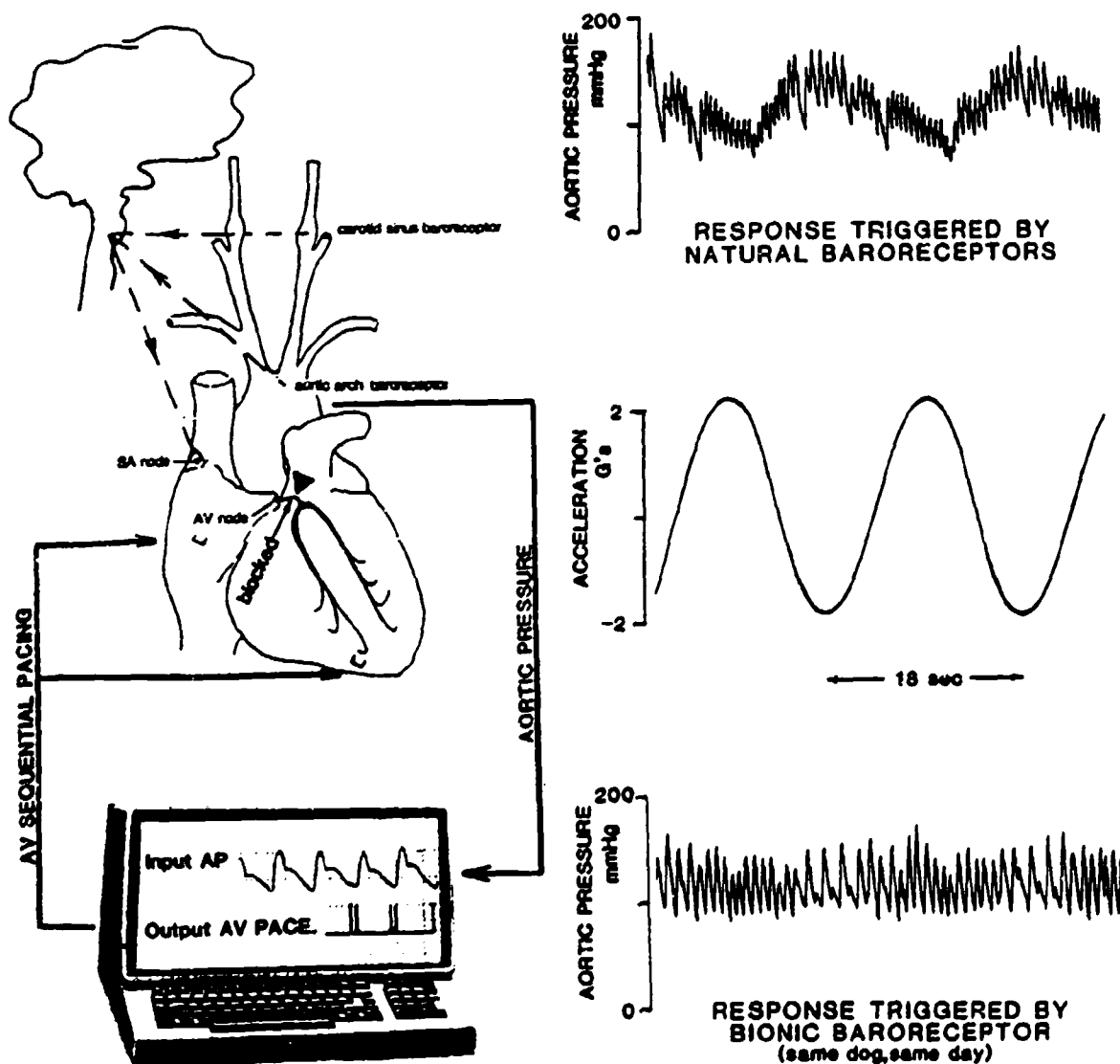


FIGURE A1. Acceleration-induced aortic pressure response triggered by the animal's natural baroreceptors (upper half) and by an aortic pressure -AV sequential pacing feedback loop (bionic baroreceptor, lower half). An example of the improvement in the control of aortic pressure during oscillatory acceleration using the microprocessor controlled feedback loop (Solid lines).

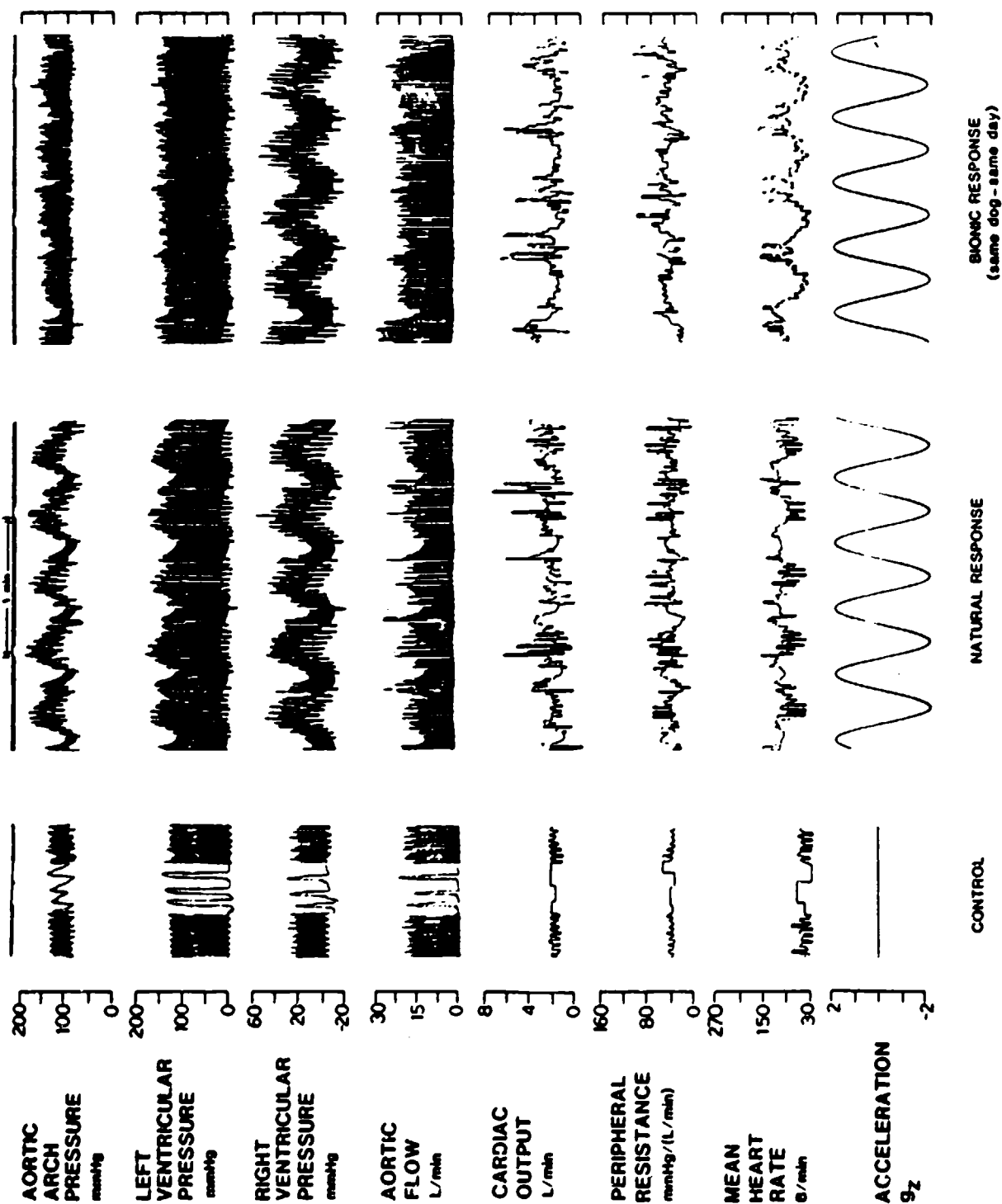


FIGURE A2. Cardiovascular response of an unblocked dog to $\pm 2 G$, 0.035 Hz acceleration with heart rate under natural baroreceptor control (middle panel) and under control of aortic arch pressure as sensed by a pressure transducer (last panel).

breathing. At an acceleration frequency of .035 Hz, oscillations in aortic pressure were 55 mm Hg and oscillations in diastolic right ventricular pressure were 30 mm Hg with the heart rate under natural control. Shifting heart rate control to the aortic pressure sensor (last panel), dramatically reduced aortic pressure oscillations to 20 mm Hg at the same frequency while allowing oscillations in right ventricular diastolic pressure to increase to 43 mm Hg. The amplitude of oscillations in the components of aortic pressure (cardiac output and peripheral resistance) were no greater under natural control than under bionic control. However, the mean cardiac output was slightly elevated during acceleration under natural control due to a 30 b/min elevation of mean heart rate at this frequency. The increase in acceleration-induced aortic pressure oscillations and the decrease in right ventricular pressure oscillations with increasing heart rate indicate a shifting of blood from the venous to the arterial circulation. Yet to be examined is the phase relationship of each of these variables with respect to acceleration that is expected to account for a part of the difference in these two modes of heart rate control during acceleration.

The response of this animal in both modes of heart rate control, to all acceleration frequencies is given in Figures A3 thru A7. In Figure A3, mean aortic pressure was the same for the two modes across the frequency range. This is a result of the design of the experiment in which the trigger for ventricular depolarization during the bionic control mode was set to reproduce the mean pressure occurring during the natural control mode. In the middle panel, maximum and minimum values of aortic pressure reached during each acceleration frequency

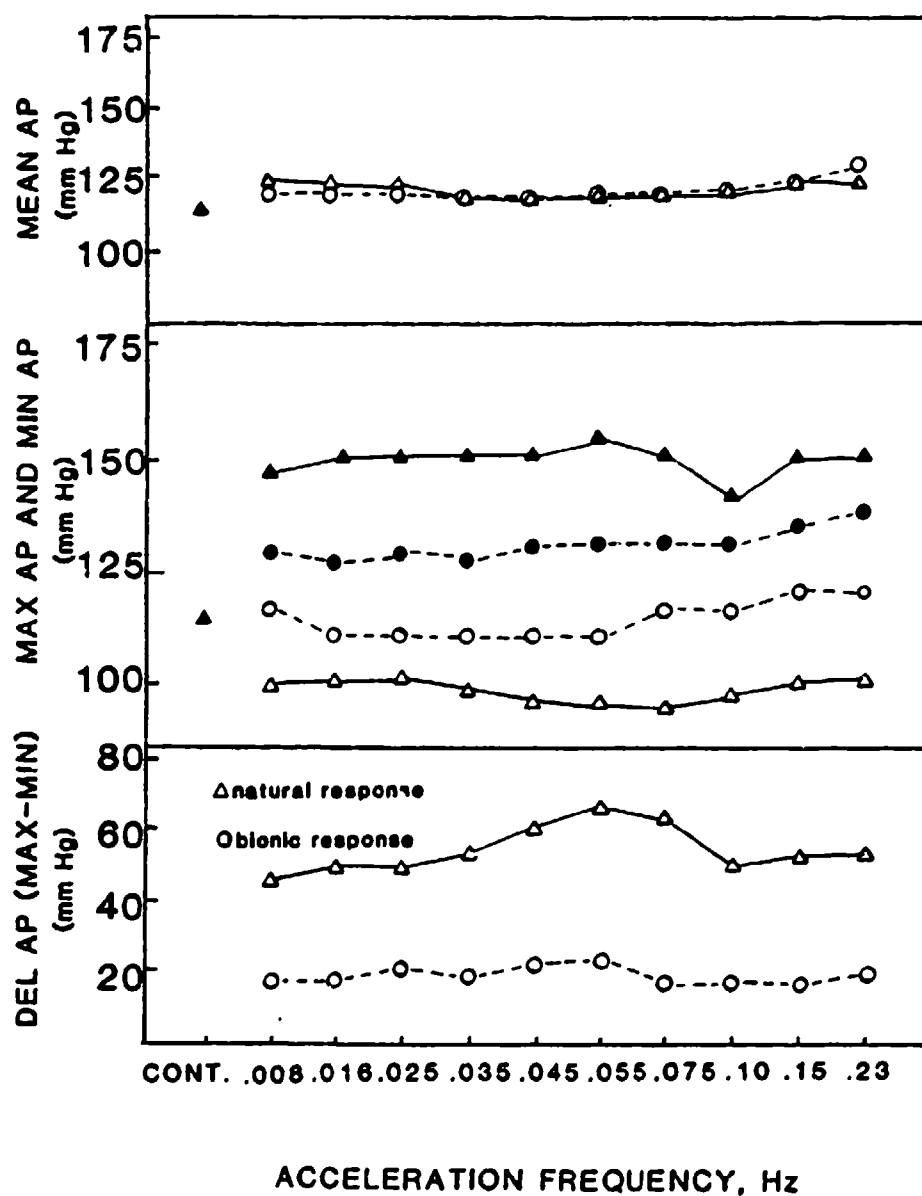


FIGURE A3. Mean, maximum and minimum and DEL aortic pressure responses to 10 acceleration frequencies for the animal in Figure A2. This data compares the animal's responses under natural heart rate control (atrial depolarization triggered by ventricular depolarization, triangles) and bionic heart rate control (atrial and ventricular depolarizations triggered by transducer-sensed aortic pressure, circles).

were greatly minimized by bionic control. The amplitude of these oscillations is given in the lower panel and a resonance type response in aortic pressure occurred as seen in the .055 Hz region in the animal's natural response. This resonance was not apparent in the animal under bionic control indicating an ability of this type of control to minimize the large hydraulic shifts of blood known to occur at this frequency (3).

Heart rate changes for this animal are shown in Figure A4. Mean heart rates between the two modes (top panel) differed by > 30 b/min at all frequencies, as did maxima and minima (middle panel). At the two lowest frequencies, bionic control of heart rate resulted in smaller oscillations of heart rate, (DEL HR, lower panel), but at all other frequencies, larger oscillations of heart rate were required to minimize the aortic pressure oscillations.

Cardiac output is shown in Figure A5. The > 30 b/min elevation in mean heart rate for the animal under natural control is evident in the slight but consistent elevation of mean cardiac output at all frequencies for natural as compared to bionic control modes. Maximum and minimum (and therefore DEL) values of cardiac output did not differ for frequencies up to .055 Hz, however for this frequency and above, the minimum value during bionic control dropped below that occurring during natural control.

Peripheral vascular resistance is shown in Figure A6. Again, very little difference was seen in this variable for both modes of control, particularly across the .035 to .075 Hz region where aortic pressure resonance occurred. However at the two lowest and four highest frequencies, maximum resistance was greater in the bionic as compared to the natural control mode.

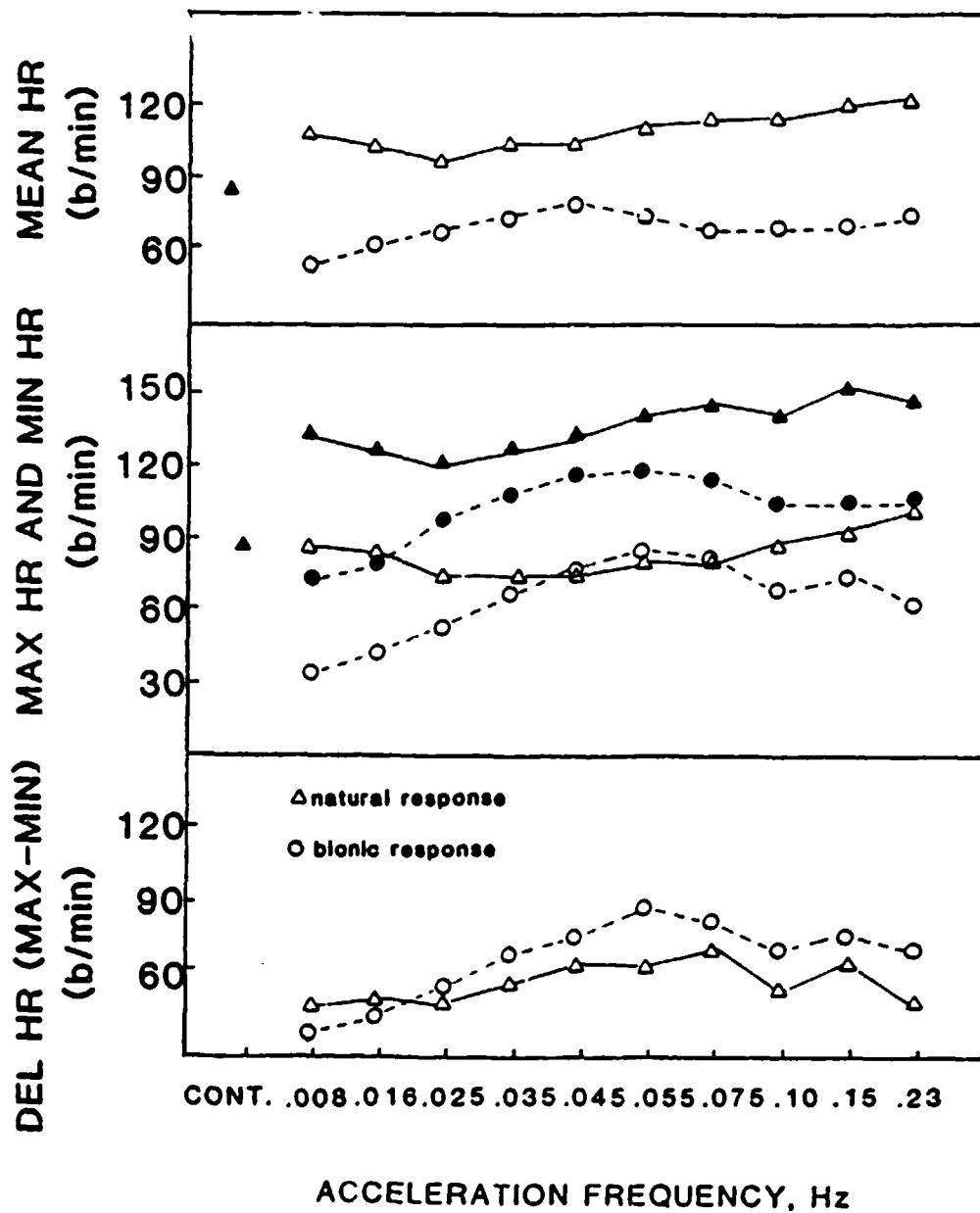


FIGURE A4. Mean, maximum and minimum and DEL heart rate responses to 10 acceleration frequencies for the animal in Figure A2. This data compares the animal's responses under natural heart rate control (atrial depolarization triggered by ventricular depolarization, triangles) and bionic heart rate control (atrial and ventricular depolarizations triggered by transducer-sensed aortic pressure, circles).

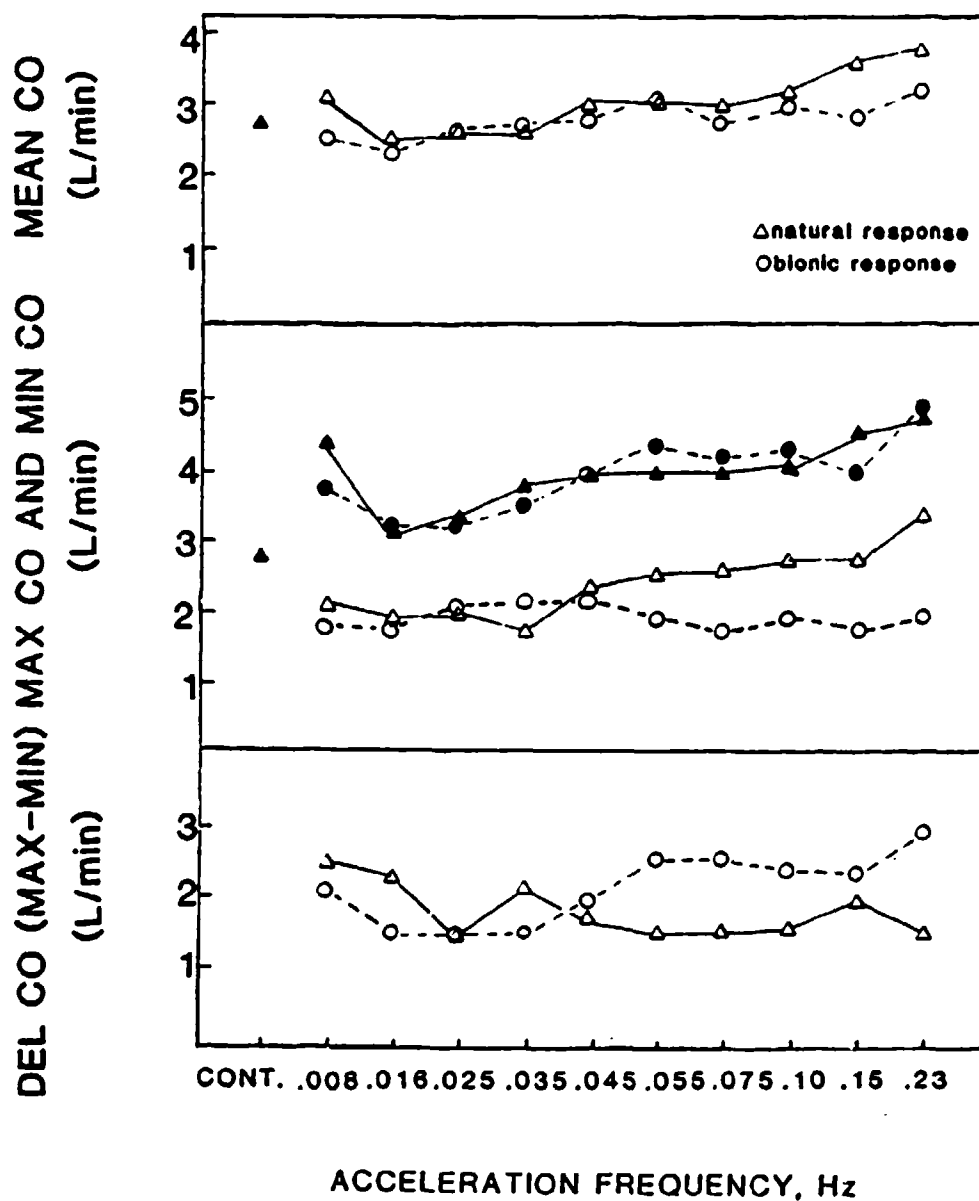


FIGURE A5. Mean, maximum and minimum and DEL cardiac output responses to 10 acceleration frequencies for the animal in Figure A2. This data compares the animal's responses under natural heart rate control (atrial depolarization triggered by ventricular depolarization, triangles) and bionic heart rate control (atrial and ventricular depolarizations triggered by transducer-sensed aortic pressure, circles).

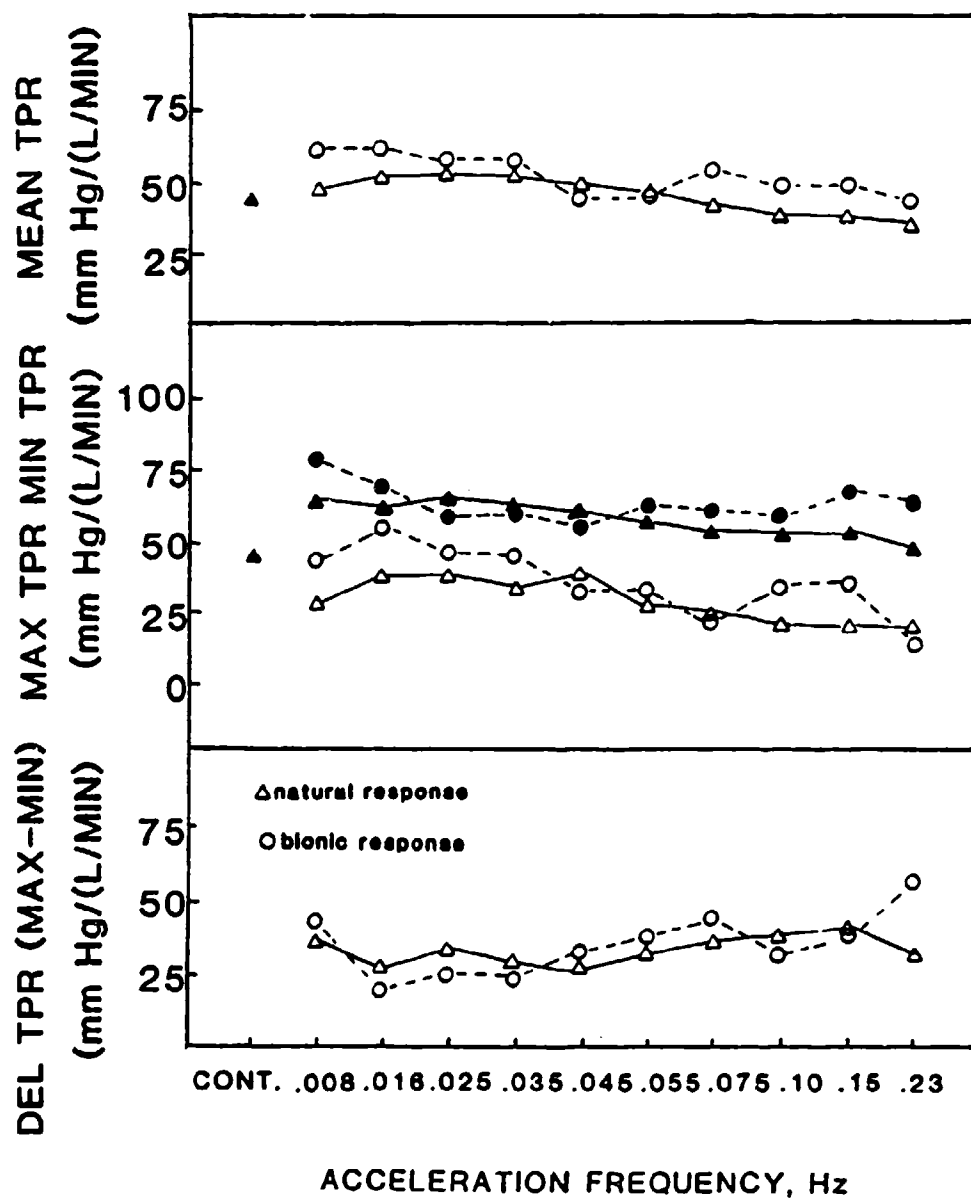


FIGURE A6. Mean, maximum and minimum and DEL peripheral resistance responses to 10 acceleration frequencies for the animal in Figure A2. This data compares the animal's responses under natural heart rate control (atrial depolarization triggered by ventricular depolarization, triangles) and bionic heart rate control (atrial and ventricular depolarizations triggered by transducer-sensed aortic pressure, circles).

Central venous pressure, measured in the right ventricle during diastole is shown in Figure A7. At all frequencies maximum, and therefore mean and DEL, right ventricular diastolic pressures were greater in the bionic control as compared to the natural control mode.

CONCLUSIONS

Ten animals were studied using this animal preparation and experimental protocol. The protocol also included an identical acceleration test in the same animal using the bionic control mode following blockade of ganglionic receptor activity in order to determine the autonomic components of this particular response. The analysis of this data even in the cursory manner presented above has not been completed, however, we can conclude from these preliminary studies that:

- 1) Use of a bionic baroreceptor to trigger A/V sequential pacing of the heart is possible and not technically difficult.
- 2) The stress of low frequency, sinusoidal, $\pm 2 G_z$ acceleration as indicated by oscillations in mean aortic pressure were reduced by approximately one half at all acceleration frequencies studied by use of the bionic, as compared to natural, stimulation of heart rate.
- 3) Magnitudes of oscillation of the components of aortic pressure (cardiac output and resistance) were not changed by using bionic, as compared to natural control of heart rate.
- 4) There was a diminished mean cardiac output during bionic control that contributed to the diminished oscillations in aortic pressure.

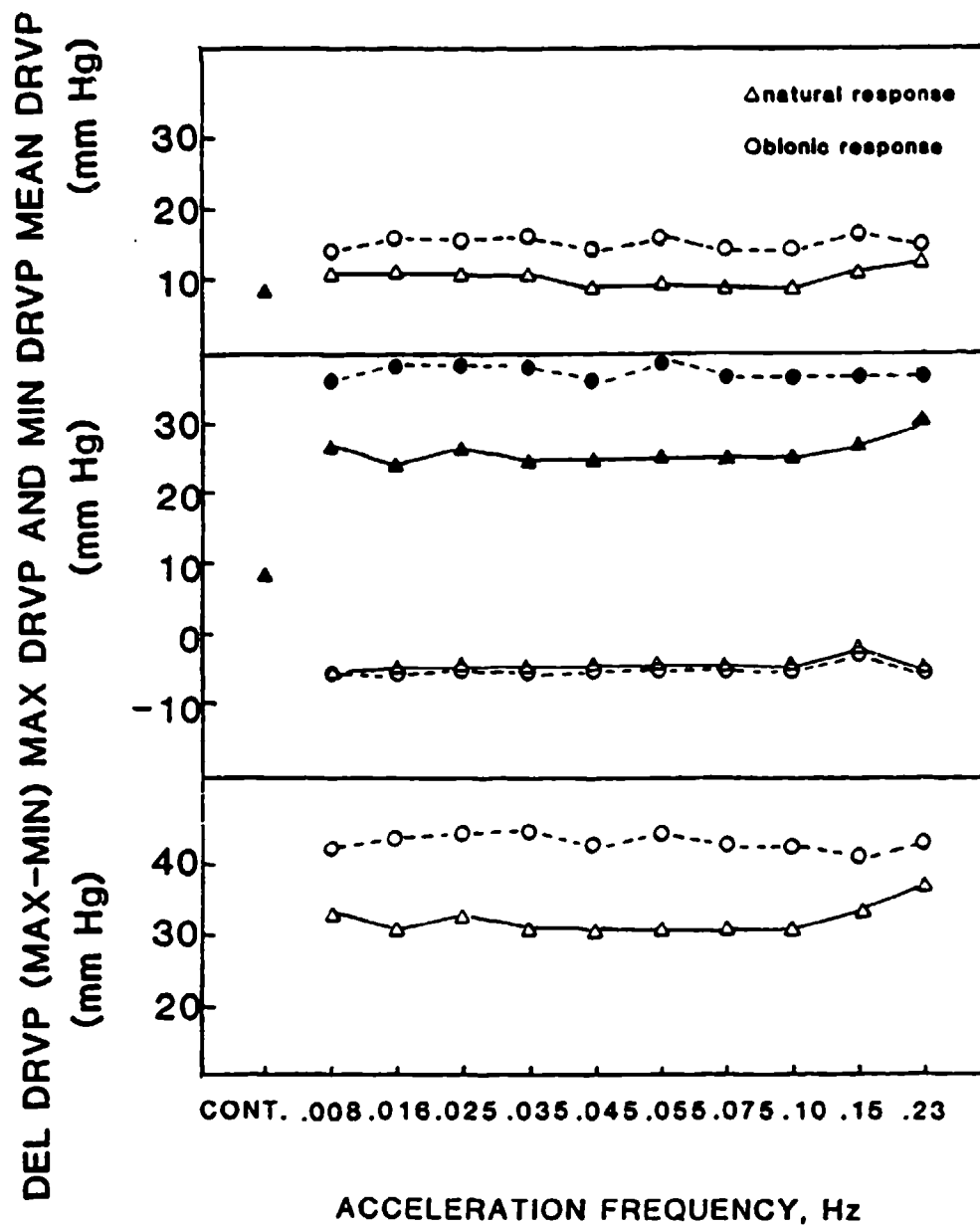


FIGURE A7. Mean, maximum and minimum and DEL diastolic right ventricular pressure responses to 10 acceleration frequencies for the animal in Figure A2. This data compares the animal's responses under natural heart rate control (atrial depolarization triggered by ventricular depolarization, triangles) and bionic heart rate control (atrial and ventricular depolarizations triggered by transducer-sensed aortic pressure, circles).

- 5) The phase relationships of resistance and cardiac output to acceleration have not yet been determined but this information is expected to provide the rest of the difference in the aortic pressure responses in these two modes.
- 6) There was an increased magnitude of oscillations in central venous pressure at all frequencies during bionic control and this increase combined with the decreased magnitude of aortic pressure oscillations indicates a shifting of blood from the arterial to venous compartments due to the lower mean heart rate in this mode.

II B. THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN STEADY STATE CARDIOVASCULAR REGULATION IN RESPONSE TO CHANGES IN HEART RATE

INTRODUCTION

A corollary study was performed on our A/V nodal blocked dogs to examine the preparation itself in terms of the steady state response of other cardiovascular variables to step input changes in heart rate. The animal preparation is detailed above in SECTION II A. The study was performed in eight supine unblocked, animals and in the same animals after ganglionic blockade of autonomic activity. The sequence of heart rates applied was randomized before the first study and the same protocol was then followed for all dogs in both states. The sequence of rates was 90, 120, 80, 60, 180, 220, 40, 200 and 90 b/min. This section of the report will compare those responses and, at a later date, a) the blocked data will be used for verifying the response of our computer model (which is a hydraulic, non feedback model) to similar changes in rate; and b) the unblocked data will be used to validate feedback mechanisms as they are added. For the present, comparisons will be made between the two states for autonomic contributions at any given heart rate and for steady state changes in either state due to increasing rate. The data was tested for both a heart rate effect, a blockade effect and a heart rate/blockade interaction using a two factor analysis of variance of the treatments-by-treatments-by subjects design. Post hoc testing was performed using Duncan Multiple Range Test when indicated by the ANOVA.

RESULTS

The most dramatic effect of increasing heart rate was on stroke volume (Figure B1) which in the unblocked animals (circles) decayed exponentially from 45.6 ml/b at a heart rate of 40 to 11.3 ml/b at a heart rate of 220 b/min. For each 20 b/min or greater increment in heart decrease in stroke volume was less drastic in the ganglionically blocked animals (triangles), dropping from 33.4 ml/b at a heart rate of 40 b/min to 9 ml/b at a heart rate of 220 b/min. In this case, 40 b/min and greater increments in heart rate produced significant decreases in stroke volume. The autonomic contribution (comparison of unblocked to blocked values at each heart rate) was significant ($p < .01$, indicated by *) at a heart rate of 40 b/min, providing a 36.5% increase over the blocked state. The autonomic contribution provided an elevation of stroke volume at the other heart rates but none were significantly greater.

Cardiac output for these same animals is given in Figure B2. Unblocked cardiac output increased with increasing rate between 40 and 120 b/min; the cardiac output at 120 b/min was significantly elevated over that at 40 and 60 b/min. Between 120 and 220 b/min there was no further change in cardiac output in the unblocked animals. In the blocked animals, output continued to rise up to 160 b/min then fell 21% at a heart rate of 220 b/min; the cardiac output at 160 b/min was significantly greater than at 40, 60, 80, 90 or 220 b/min. The autonomic contribution to cardiac output, which was of course restricted to inotropic changes, caused an elevation of cardiac output at all heart rates that was significant at 40 b/min,

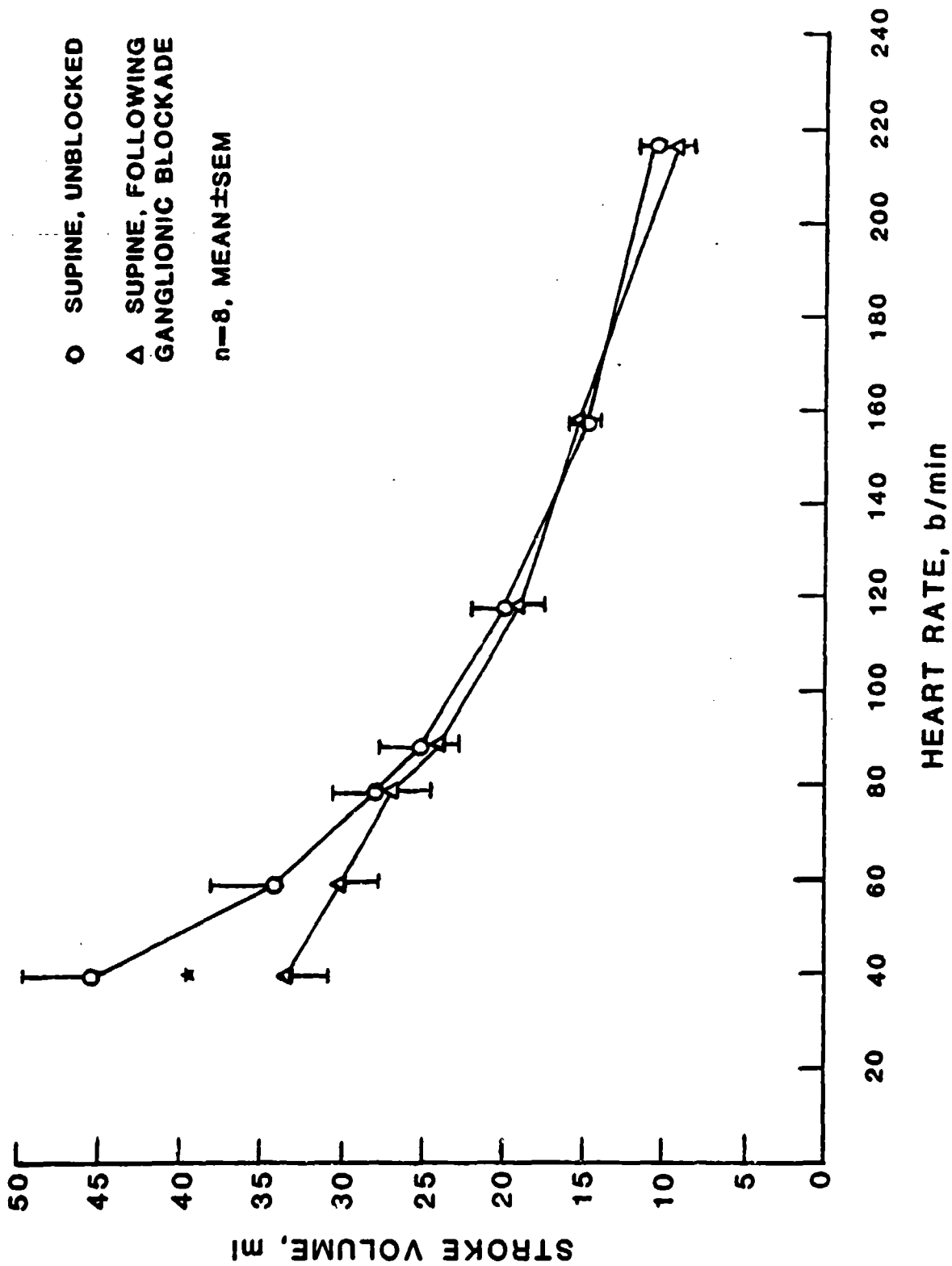


FIGURE B1. Stroke volume responses to increasing heart rate for a group of 8 supine animals in the unblocked state (circles) and following ganglionic blockade (triangles). Significant changes with increasing rate are discussed in the text, significant changes due to autonomic contributions are indicated by asterisks.

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60 b/min and at 220 b/min.

Diastolic right ventricular pressure (our indicator of venous return) is given in Figure B3. In both unblocked and blocked animals central venous pressure had a minimum value at 90 b/min and a maximum value at 40 b/min. In the unblocked animals, the minimum value occurred at 90 b/min and was significantly lower than that at 40 b/min or at 220 b/min, while the maximum value at 40 b/min was significantly greater than at all other heart rates. In the blocked dogs, the same was true except that the maximum value at 40 b/min was significantly greater than that at heart rates of 80 b/min and above. The autonomic contribution was a significant lowering of central venous pressure at all heart rates ranging from 2.0 mm Hg at a heart rate of 160 b/min to 4.4 mm Hg at a heart rate of 60 b/min.

Peripheral vascular resistance for these animals is shown in Figure B4. In the unblocked animals, resistance had a maximum value at a heart rate of 40 b/min and a minimum value at 120 b/min. The maximum value at 40 b/min was significantly greater than that at heart rates of 120 and above. In the blocked dogs a different trend was evident with the maximum value of resistance occurring at 120 b/min, falling off with increasing or decreasing rate. This maximum was not significant; however in 7 of the 8 animals the maximum blocked resistance value occurred at either 90 b/min or 120 b/min and in the other dog a second highest value occurred at 120 b/min. Autonomic contributions to increase vascular resistance were evident at all heart rates and were significant at 40 and 60 b/min.

The interaction of all of these variables to regulate aortic arch pressure is shown in Figure B5. In the unblocked animals, aortic pressure was significantly lower at 40 and 60 b/min than at higher

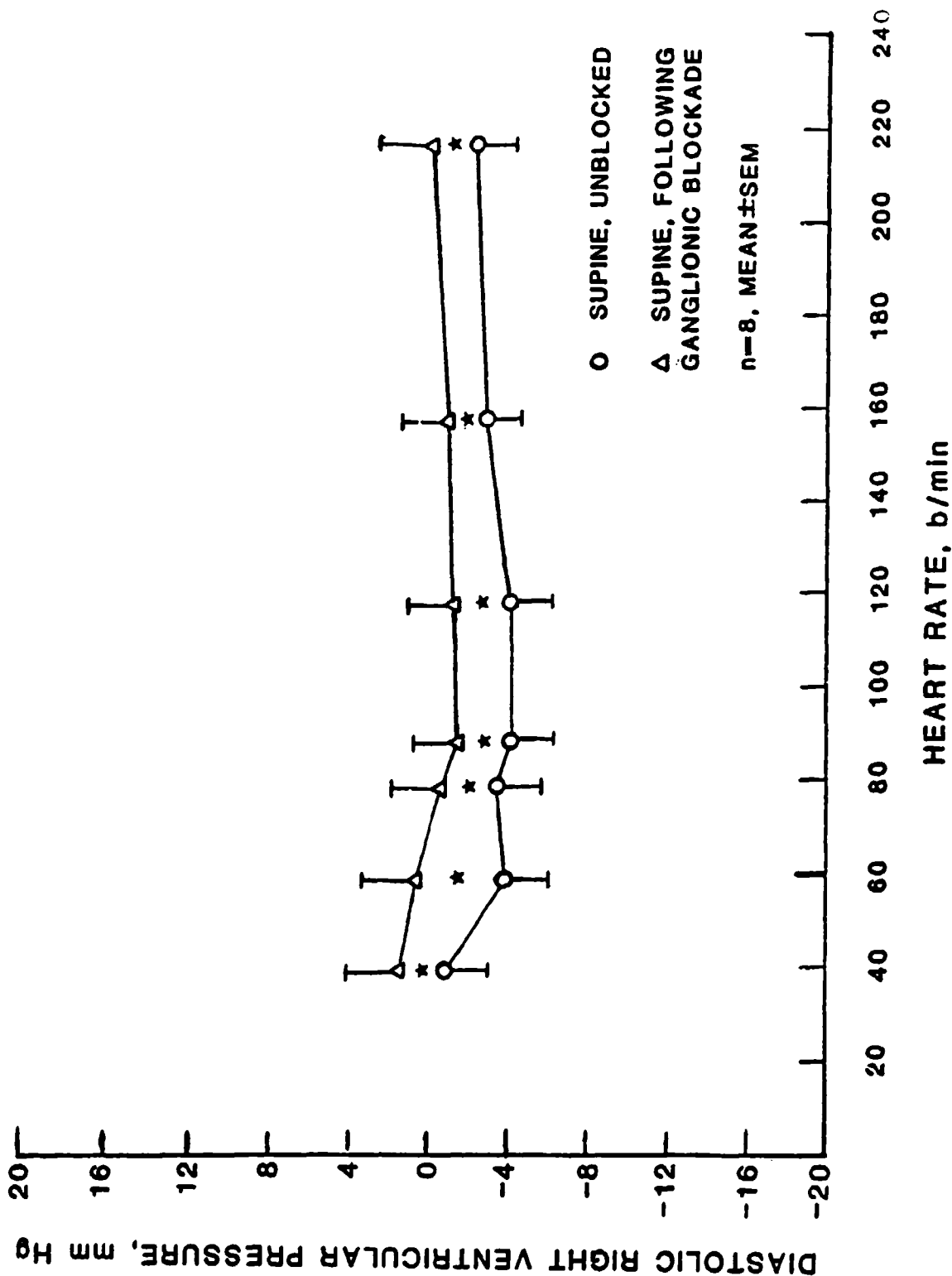


FIGURE B3. Diastolic right ventricular pressure responses to increasing heart rate for a group of 8 supine animals in the unblocked state (circles) and following ganglionic blockade (triangles). Significant changes with increasing rate are discussed in the text, significant changes due to autonomic contributions are indicated by asterisks.

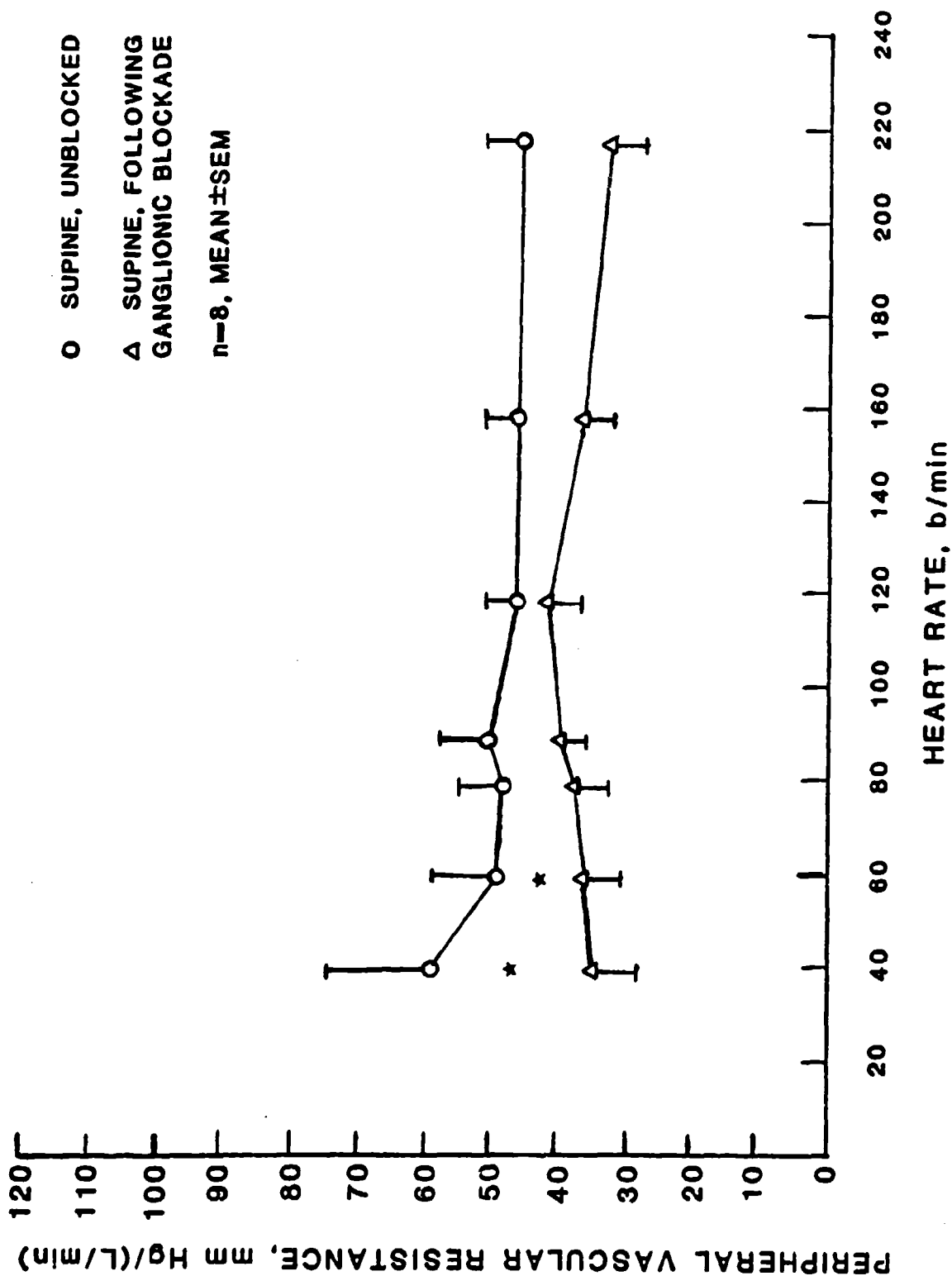


FIGURE B4. Peripheral vascular resistance responses to increasing heart rate for a group of 8 supine animals in the unblocked state (circles) and following ganglionic blockade (triangles). Significant changes with increasing rate are discussed in the text, significant changes due to autonomic contributions are indicated by asterisks.

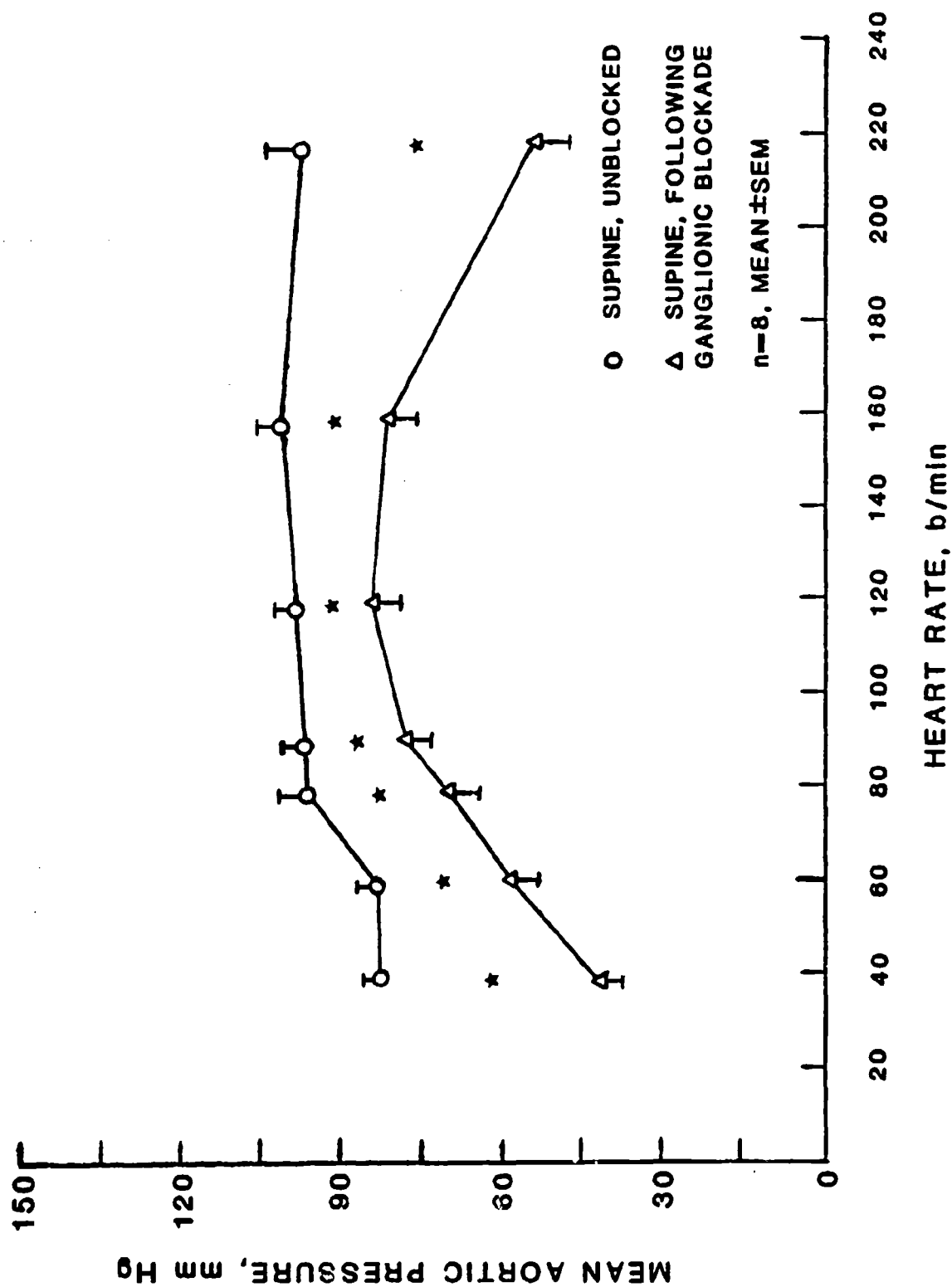


FIGURE B5. Mean aortic pressure responses to increasing heart rate for a group of 8 supine animals in the unblocked state (circles) and following ganglionic blockade (triangles). Significant changes due to increasing rate are discussed in the text, significant changes due to autonomic contributions are indicated by asterisks.

heart rates. In the blocked dogs a very different trend was apparent with a maximum value of aortic pressure at a heart rate of 120 b/min. This maximum value was significant with respect to values at 40, 60, 80 and 220 b/min. The autonomic contribution to maintain aortic pressure was significant at all heart rates.

CONCLUSIONS

- 1) The effect of increasing heart rate from 40 to 120 b/min in unblocked dogs was to lower stroke volume, peripheral resistance and central venous pressure, while increasing cardiac output and aortic pressure. From 120 to 220 b/min there was no major change in these variables except for further decreases in stroke volume.
- 2) In ganglionically blocked dogs, increasing heart rate from 40 to 120 b/min lowered stroke volume and central venous pressure while increasing resistance, cardiac output and mean aortic pressure. Further increase of heart rate from 120 to 220 b/min resulted in further decreases in stroke volume with a reversal in trends of all other variables; central venous pressure rose while peripheral resistance, cardiac output and mean aortic pressure all decreased.
- 3) In the ganglionically blocked dogs, the peak in aortic pressure at 120 b/min resulted from peaking peripheral resistance and cardiac output responses in the same range. When the actual peak values from each of the eight animals were averaged, the peak pressure occurred at 132 b/min with peak resistance at 109 b/min and peak cardiac output at 145 b/min.

4) The contributions of autonomic effector activity were significant for all variables at some heart rates and for some variables at all heart rates:

- a. Mean values of aortic pressure were significantly elevated and mean levels of central venous pressure were significantly depressed by autonomic activity at all heart rates.
- b. Cardiac output, peripheral resistance and stroke volume were elevated by autonomic effector activity at all heart rates but significant elevation of stroke volume occurred only during the 40 b/min test while significant elevations of cardiac output and resistance occurred at 40 and 60 b/min.

II C. STEADY STATE CARDIOVASCULAR RESPONSES TO COMBINATIONS OF INCREASED HEART RATE AND INCREASED +GZ ACCELERATION

This study was designed to separate the effects of increasing +G_z acceleration from the effects of increasing heart rate on the steady state responses of other cardiovascular variables. As in the previous study, II. B, the steady state responses to 3 min each of 7 randomly applied heart rates from 40 to 220 b/min were determined in supine (0 G_z) animals. These animals were then brought to +1 G_z on our centrifuge and the heart rate sequence was repeated. Lastly, the animals were brought to +2 G_z with the heart rate sequence repeated again. The animal preparation was the chronically instrumented, A/V sequentially paced (70 to 100 msec delay), tranquilized dog detailed in the methods section of SECTION II. A above.

RESULTS

Steady state, mean aortic pressures at 40, 60, 80, 90, 120, 160, and 220 b/min for 8 unblocked animals at 0 G_z (circles), +1G_z (triangles) and +2 G_z (squares) are given in Figure C1. For all three tests, aortic pressure rose significantly ($p < .01$) as heart rate was increased from 40 to 90 b/min. There was no difference between 0, +1 and +2 G_z at any heart rate indicating effective steady state, aortic pressure regulation by these animals for up to +2 G_z acceleration.

The components of aortic pressure regulation, cardiac output and peripheral resistance did however indicate differences with acceleration levels.

Cardiac output for these 8 animals during the same tests is given in Figure C2. For the 0 G_z animals there was a significant increase in cardiac output up to a heart rate of 120 b/min with no further

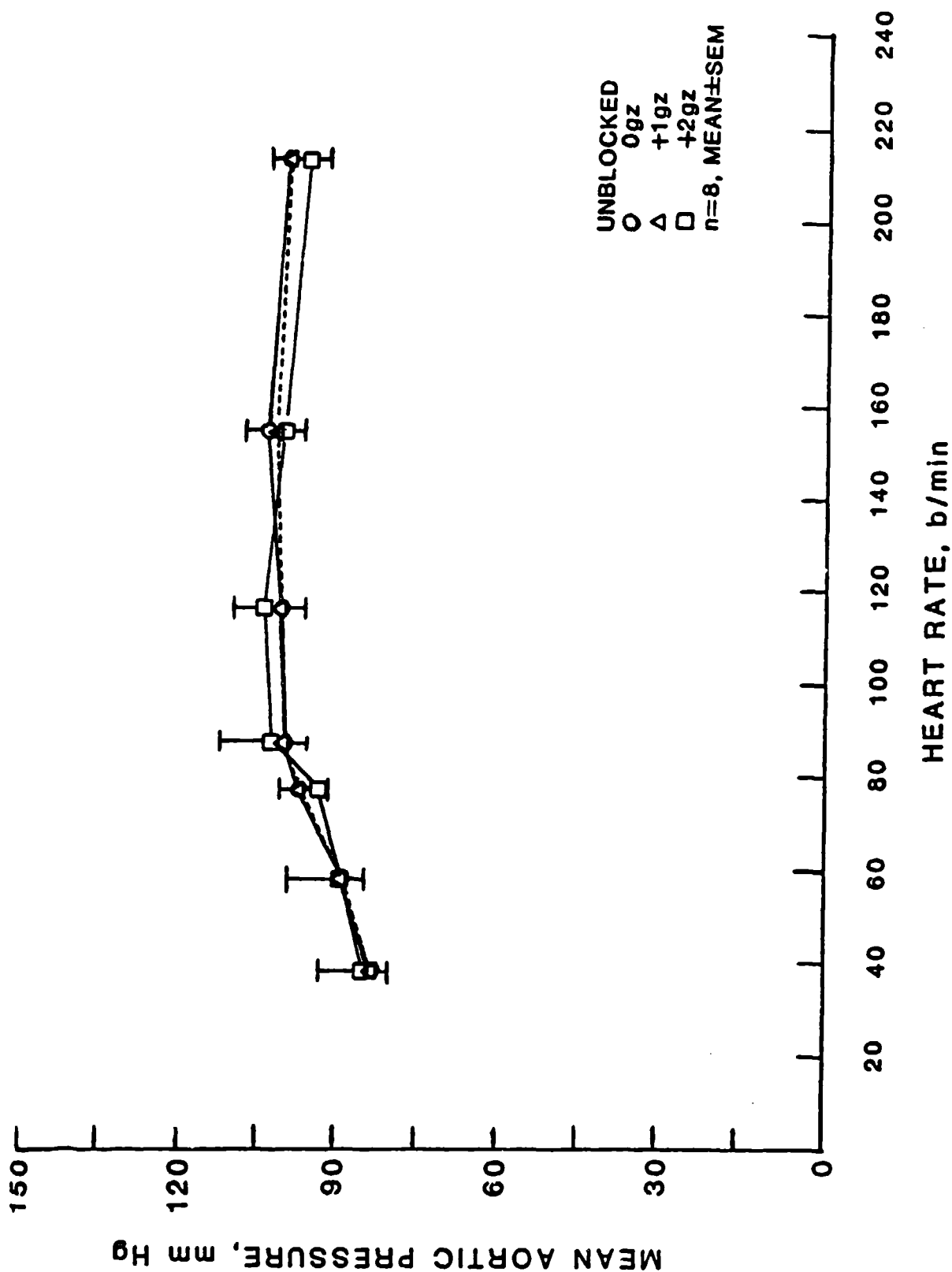


FIGURE C1. Mean aortic pressure responses to increasing heart rate for a group of 8 unblocked dogs at 0 G_Z (circles) at +1 G_Z (triangles) and at +2 G_Z (squares). Significant changes with heart rate and/or acceleration levels are discussed in the text.

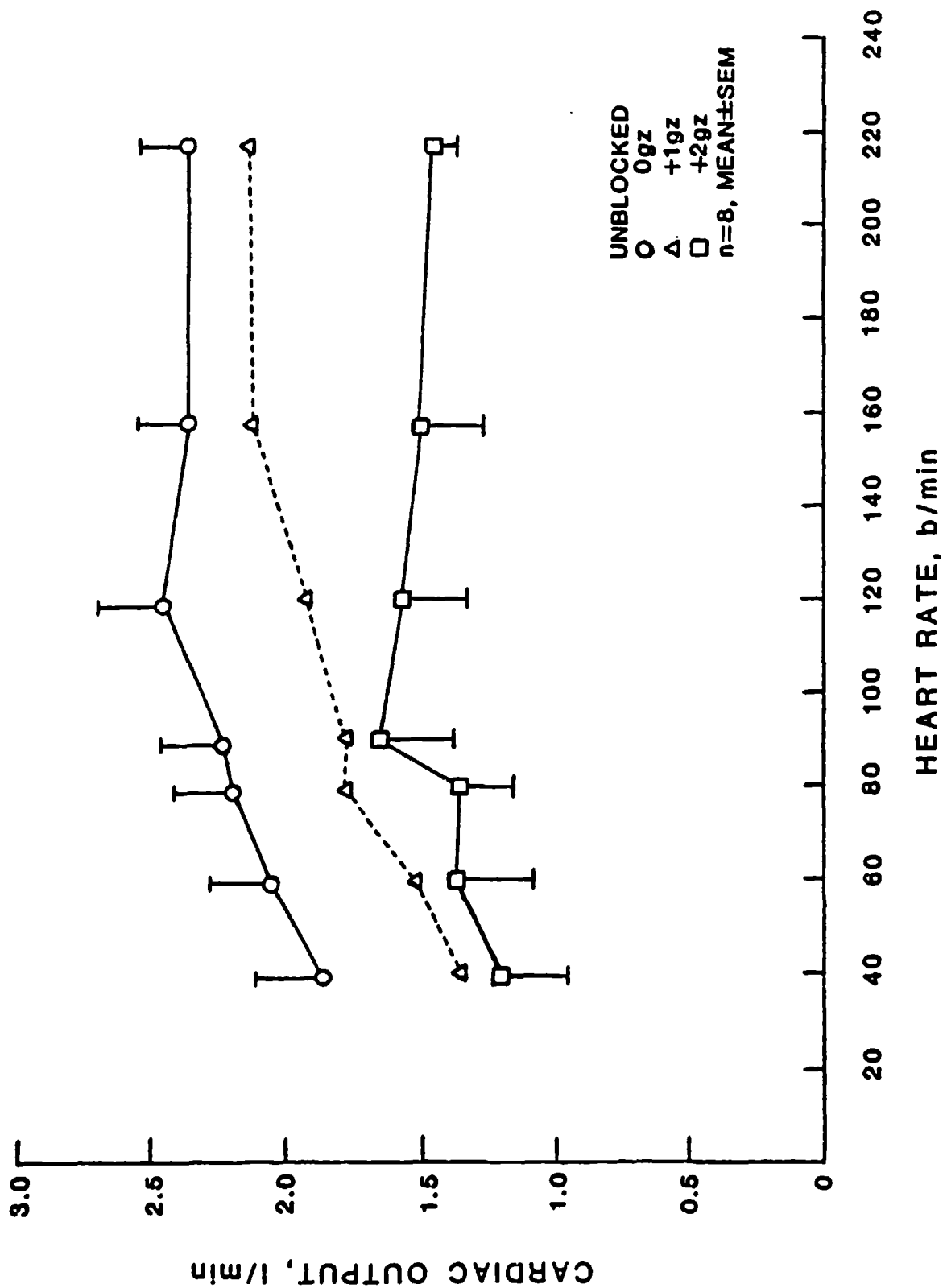


FIGURE C2. Cardiac output responses to increasing heart rate for a group of 8 unblocked dogs at 0 G_r (circles) at +1 G_r (triangles) and at +2 G_r (squares). Significant changes with heart rate and/or acceleration levels are discussed in the text.

changes for heart rates up to 220 b/min. For the same animal at +1 G_z , cardiac output continued to increase as heart rate increased up to 160 b/min, and in +2 G_z animals, maximum cardiac output was reached at a heart rate of 90 b/min. Differences between 0 G_z and +2 G_z cardiac outputs were significant at all heart rates and ranged from a 33% drop in cardiac output during +2 G_z at a heart rate of 40 b/min to a 40% drop at a heart rate of 220 b/min. The +1 G_z cardiac output was significantly lower than the 0 G_z output up to 160 b/min and was significantly greater than the +2 G_z output at 160 b/min and higher.

The cardiac output differences seen as a result of +1 and +2 G_z acceleration were totally due to stroke volume differences since heart rates were the same. The stroke volume response for these animals is given in Figure C3. For all three tests there was an exponential decay of stroke volume as a function of increasing heart rate. As in the case of cardiac output, the decrease in stroke volume as a result of +2 G_z acceleration was significant at all heart rates when compared to the 0 G_z state, with a decrease of 37% at 40 b/min and a decrease of 39% at 220 b/min. The decrease in stroke volume as a result of +1 G_z acceleration was significant for heart rates up to 120 b/min with a 28% decrease at a heart rate of 40 b/min and an 11% decrease at 220 b/min.

The compensation for the decrease in cardiac output resulting from +1 G_z and +2 G_z acceleration effects on stroke volume was provided by peripheral vascular resistance (Figure C4). For all three acceleration levels, an elevated resistance was observed for the lower heart rates; the time in which cardiac outputs and

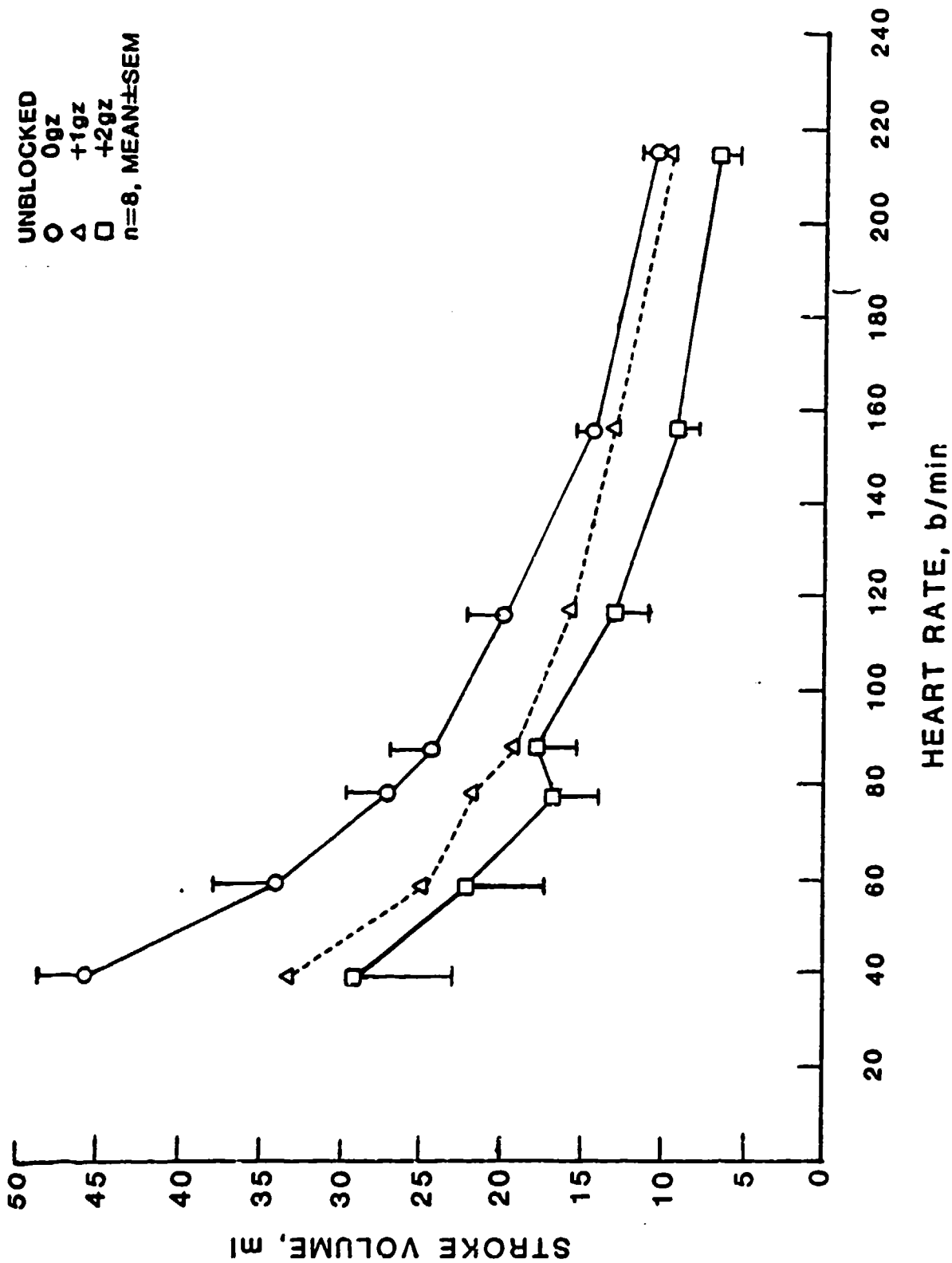


FIGURE C3. Stroke volume responses to increasing heart rate for a group of 8 unblocked dogs at 0 G_z (circles) at +1 G_z (triangles) and at +2 G_z (squares). Significant changes with heart rate and/or acceleration levels are discussed in the text.

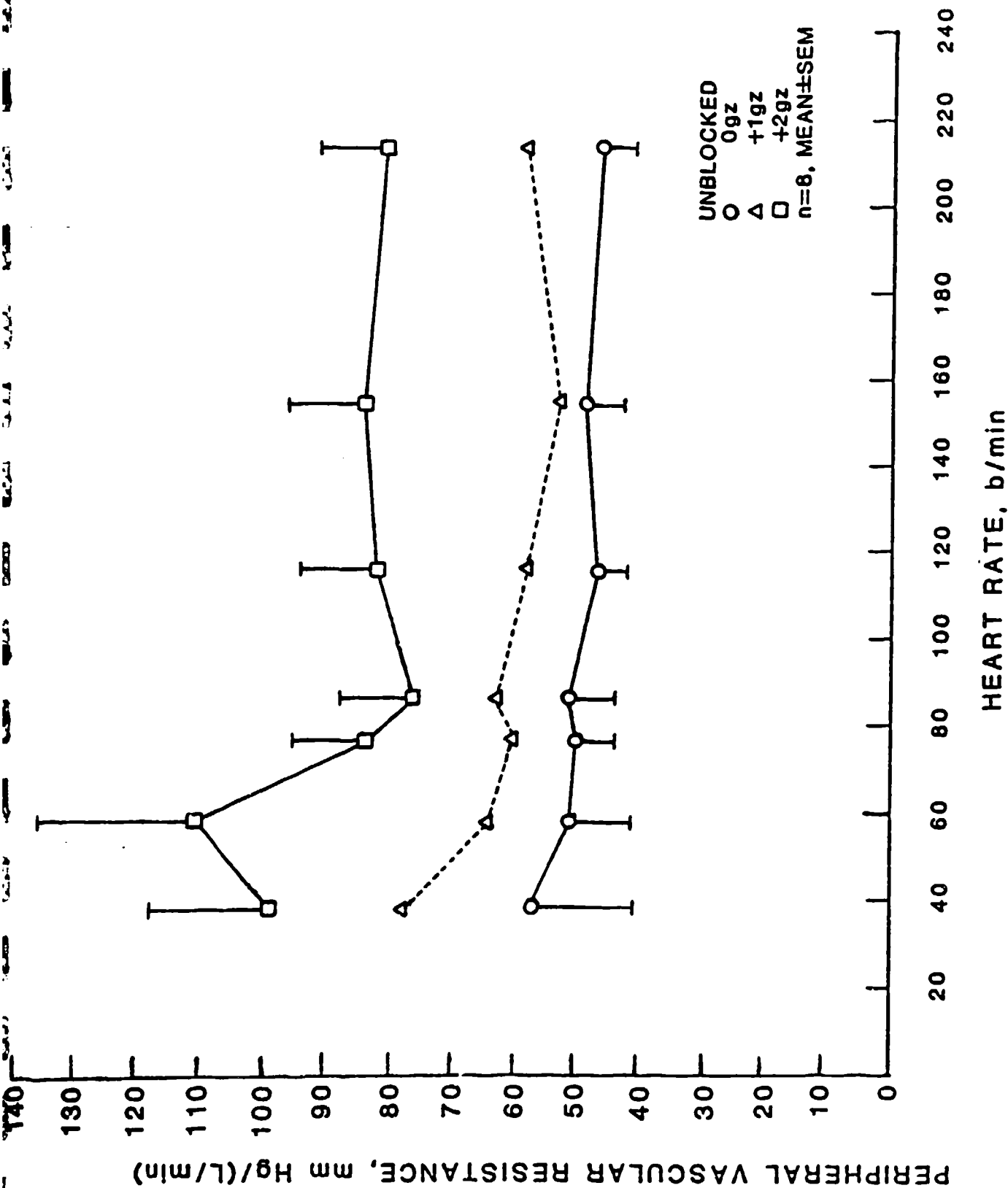


FIGURE C4. Peripheral vascular resistance responses to increasing heart rate of a group of 8 unblocked dogs at 0 G_z (circles) at +1 G_z (triangles) and at +2 G_z (squares). Significant changes with heart rate and/or acceleration levels are discussed in the text.

pressures were lowest. Significantly increased resistance during +2 G_z as compared to 0 G_z was found at all heart rates. During +1 G_z the increase with respect to 0 G_z was significant at all heart rates except 160 b/min.

Diastolic right ventricular pressures for the same animals during the same tests are given in Figure C5. During 0 G_z and +1 G_z testing, this measure of central venous pressure decreased with increasing heart rate up to a heart rate of 120 b/min, with no further change for heart rates up to 220 b/min. For both 0 G_z and +1 G_z the right ventricular diastolic pressure at a heart rate of 40 b/min was significantly greater than at any higher heart rate. The decrease in diastolic ventricular pressure during +2 G_z at the highest heart rate (220 b/min) was significant when compared to the other heart rates at this G level. The decrease in pressure resulting from both +1 G_z and +2 G_z acceleration was significant at the lowest (40 b/min) and highest (220 b/min) heart rates when compared to the 0 G_z state.

CONCLUSIONS

1. Steady state levels of mean aortic pressure were the same at 0, +1 and +2 G_z acceleration levels:
 - a. All three pressures rose ~18 mm Hg as heart rates increased from 40 to 120 b/min.
 - b. There was no further change in mean pressure as heart rates increased from 120 to 220 b/min.
2. There was a combined effect of increasing heart rate and increasing + G_z that resulted in an 86% decrease in stroke volume at +2 G_z and a heart rate of 220 b/min when compared to stroke volume at 0 G_z and 40 b/min.
3. The effect of reduced stroke volume due to +2 G_z resulted in

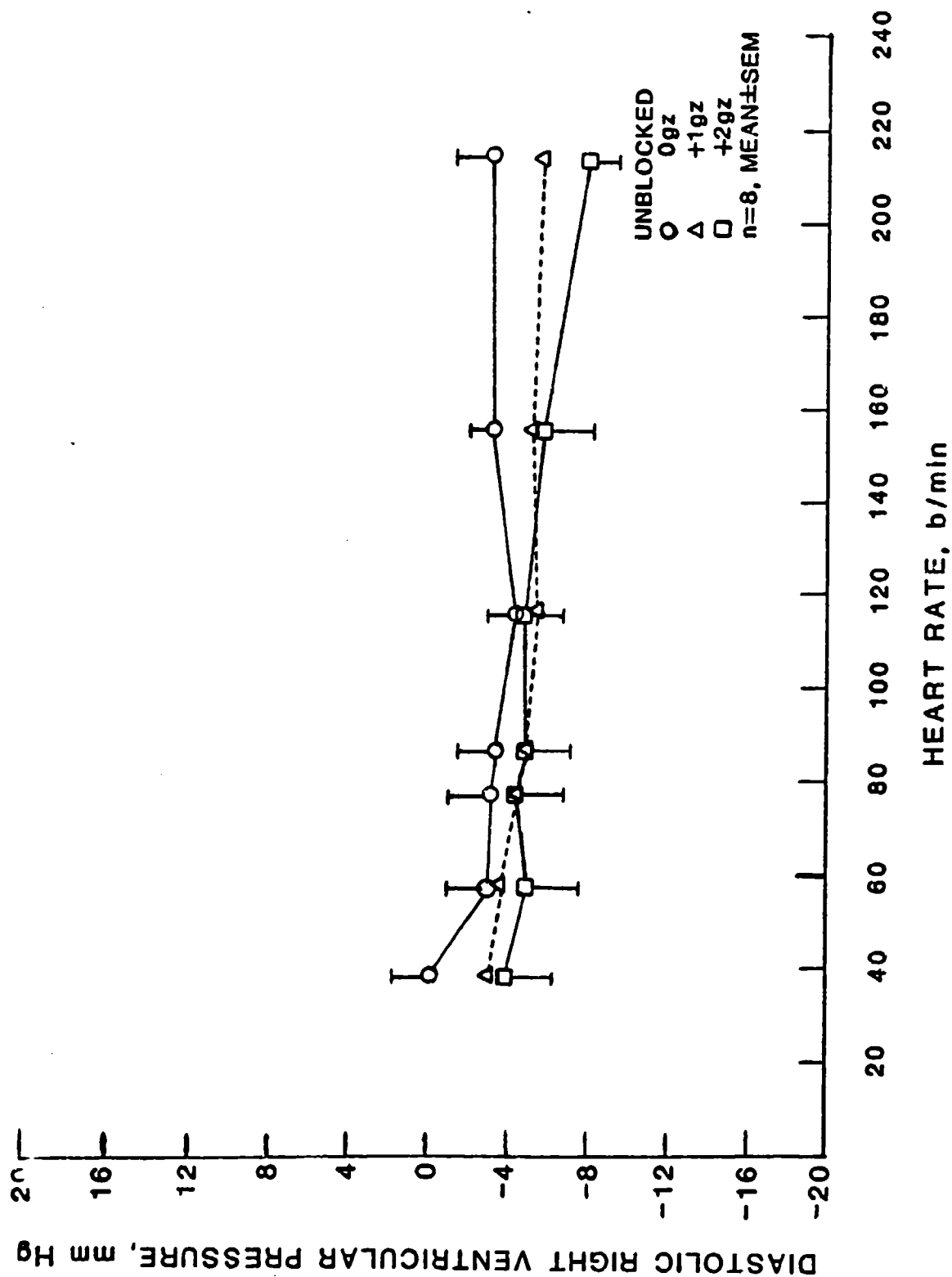


FIGURE C5. Diastolic right ventricular pressure responses to increasing heart rate for a group of 8 unblocked dogs at 0 G_z (circles) at +1 G_z (triangles) and at +2 G_z (squares). Significant changes with heart rate and/or acceleration levels are discussed in the text.

an average reduction of cardiac output by 33% at all heart rates when compared to 0 G_z cardiac outputs at the same heart rates.

4. The compensation for the reduction in cardiac output due to +2 G_z acceleration was provided by an average increase of ~83% in peripheral vascular resistance at all heart rates.
5. The reduction of stroke volume due to increasing levels of + G_z was attributed to loss of venous return due to the compliance of the venous system. This reduction in venous return was substantiated by reduction of diastolic right ventricular pressure at the increased + G_z levels.

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**III. CARDIOVASCULAR RESPONSES TO
UNTRAINED AND ENDURANCE TRAINED
DOGS TO OSCILLATORY BLOOD VOLUME SHIFTS**

DISSERTATION

JOHN B. CHARLES

1983

ABSTRACT OF DISSERTATION

The purpose of this study was to assess the effects of endurance training on the cardiovascular adjustments to low-frequency oscillations in central blood volume. The responses of a group of dogs that was endurance trained by treadmill running were compared to those of a group of untrained dogs.

Each animal was placed on a centrifuge which generated a sinusoidally varying spinal axis acceleration. This produced oscillations in central blood volume and pressure which stimulated the reflex responses of interest. Ten discrete acceleration frequencies, from 0.008 to 0.23 Hz, were tested.

Chronic and acute instrumentation measured aortic arch blood pressure (AP), right and left ventricular pressures (RVP and LVP, respectively), heart rate (HR), cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR). Off-line computer analysis used a Fast Fourier Transform of each variable to calculate its average value, the amplitude of its first harmonic, and phase angle of its first harmonic at each frequency. A two factor, mixed design analysis of variance and the Newman-Keuls multiple range test determined statistical signifi-

cance between group means at individual frequencies.

Both groups of animals maintained comparable levels of AP and CO. The trained group had a lower mean SV ($p < 0.05$) from 0.016 to 0.045 Hz, and a lower mean diastolic LVP ($p < 0.05$) at all the frequencies tested. Diastolic RVP was the same, indicating that blood volume was comparable in both groups. The LVP discrepancy may reflect a pulmonary vascular resistance difference due to training. The HR first harmonic was much larger ($p < 0.01$) in the trained animals at 0.016 to 0.035 Hz, and the trained animals' TPR first harmonic was delayed ($p < 0.05$) at 0.016 Hz, compared to the untrained group. The TPR data suggest a lag in the trained dogs' peripheral vascular responses to carotid sinus baroreceptor stimulation. The location of this training effect in the baroreceptor reflex arc was not determined in this study.

The results indicate that the endurance trained dogs could not rely on their peripheral resistance mechanisms to counter the acceleration-induced blood volume shifts. Therefore, they used their heart rate reserve capacity to regulate and maintain blood pressure.

John B. Charles

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INTRODUCTION

Many investigations have demonstrated that the regulation of the cardiovascular system is modified by endurance exercise conditioning (reviewed in: Claussen, 1977; Scheuer and Tipton, 1977; Blomqvist and Saltin, 1983). In the majority of these studies, a form of exercise has been the provocative stress in assessing the effects of endurance training on cardiovascular regulation. Only a few have used a nonexercise provocation. A nonexercise stress usually produces a passive translocation of blood volume within the vasculature, as elicited by head-up tilt (Klein *et al.*, 1969a,b; Mangseth *et al.*, 1980; Clifford *et al.*, 1981), lower body negative pressure (Luft, 1980; Tipton *et al.*, 1982), and centrifugal acceleration (Cooper and Leverett, 1966; Klein *et al.*, 1969a,b). These studies have determined the effects of endurance training on the individual components of the cardiovascular regulatory mechanism.

Almost all of the previous investigations have quantified the cardiovascular response to stress by considering only the physiological manifestations of some endpoint--usually, impending syncope. Thus, they have neglected the information content of the pattern of the response to the provocation. A more thorough analysis

would include the information contained in the responses of, for example, untrained and endurance trained subjects to repetitive stresses, which cause transient blood volume shifts. Recent studies (Taylor, 1966; Brown and Taylor, 1971; Marquis, 1978; Brown *et al.*, 1981; Knapp *et al.*, 1982) have demonstrated the value of time-dependent perturbations in delineating the contributions of the components of cardiovascular regulation. These techniques can recover the information otherwise lost, and provide insight into the changes in cardiovascular control which are associated with endurance training.

This chapter examines some of the changes in cardiovascular regulation concomitant with aerobic conditioning as assessed by non-exercise stresses. Then, the frequency response characteristics of the cardiovascular system, as determined by isolated organ and whole-body experiments, are reviewed. Finally, the application of this approach in differentiating between sedentary and endurance trained subjects is discussed.

Cardiac and Peripheral Vascular Effects of Chronic Exercise.

Endurance training's effects on cardiac regulation include reduced heart rate and increased stroke volume at rest and during exercise, and increased cardiac output with maximal exercise (Scheuer and Tipton, 1977). Condi-

tioning doesn't significantly change the mean arterial blood pressure during exercise, implying that the increase in cardiac output with training is associated with a decrease in total peripheral resistance (Claussen, 1977). During maximal exercise, highly trained athletes may have a total peripheral resistance that is 4.5 times smaller than that of untrained subjects (Claussen, 1977). As the heart rate response to exercise diminishes with training, so does the vasoconstriction of the abdominal viscera and coronary beds, suggesting a decreased sympathetic response to the exercise stress (Claussen, 1977; Liang and Stone, 1983).

The mediation of the heart rate response to exercise has yet to be completely specified. The role of the autonomic nervous system is clearly established, since cardiac denervated dogs failed to develop resting and exercise bradycardia with endurance training, while their sham-operated cohorts did (Ordway *et al.*, 1982). There is evidence for a diminished sympathetic tone both at rest and during exercise (Scheuer and Tipton, 1977). Enhanced parasympathetic (vagal) activity is also implicated (Scheuer and Tipton, 1977; Talan *et al.*, 1980).

The endurance training effects may be due, in part, to changes in the reflex control of heart rate and blood pressure. There is evidence that the responses of these variables to changes in carotid sinus transmural pressure are reduced with aerobic conditioning (Stegemann *et al.*,

1974; Clifford et al., 1981). However, heart rate responses to exogenously infused vasoactive substances reveal no training differences (Ordway, et al., 1982).

Comparisons of the Responses of Untrained and Endurance Trained Subjects to Nonexercise Stresses.

There are few documented comparisons of the responses of untrained and endurance trained subjects to nonexercise stresses. Those extant usually involve the shifting of blood volume out of the upper body and into the abdominal viscera and legs. This has been accomplished by head-up tilting, (Klein et al., 1969a,b; Mangseth et al., 1980; Clifford et al., 1981), lower body negative pressure (Luft, 1980; Tipton et al., 1982), and "headward" acceleration (i.e., blood shifted out of the upper and into the lower portions of the body) on a centrifuge (Cooper and Leverett, 1966; Klein et al., 1969a,b). These studies have provided a different perspective on the adaptations to regular exercise than those using a form of exercise itself as the stress.

Training Effects on Responses to Head-up Tilting.

Investigations into the differences in orthostatic tolerance which may be linked to the level of aerobic conditioning have taken two forms: comparisons of the

tolerance of untrained and trained subjects (Klein *et al.*, 1969a,b; Mangseth *et al.*, 1980; Luft, 1980; Clifford *et al.*, 1981); and, determinations of the trained states of nonfainters and fainters on tilt table tests (Shvartz and Meyerstein, 1972; Mangseth *et al.*, 1980). Shvartz and Meyerstein (1972) used a 70-degree head-up tilt lasting 20 minutes to classify a group of subjects as nonfainters (n=30) or fainters (n=4). Since there were no differences between the groups in maximum oxygen uptake, they concluded that orthostatic tolerance was unaffected by trained state, at least as reflected in oxygen consumption. The small size of the group of fainters makes any statistical comparison tenuous, however. In a more balanced study, Mangseth *et al.* (1980) used a 30-minute, 70-degree head-up tilt to stress groups of 8 known fainters and 8 non-fainters. The fainters, who succumbed after an average of 18 minutes, had a maximum oxygen uptake that averaged 57.1 ± 3.3 (SEM) ml./kg./min. compared to 46.9 ± 2.0 (SEM) for the nonfainters ($p < 0.05$). Thus, this study suggests that a lower orthostatic tolerance is associated with a higher degree of cardiovascular fitness.

In two studies, Klein *et al.* (1969a,b) compared healthy, untrained young men to age-matched, endurance-trained athletes (runners, skiers, and skaters). The groups had maximum oxygen uptakes of 43.9 and 64.9 ml./kg./min., respectively. A 20-minute, 90-degree head-up tilt produced a heart rate increase of 30% in both

groups, although the athletes' resting and stressed heart rates were 22 % higher ($p < 0.001$). However, both groups had a similar rate of syncope (14% and 17%, respectively), suggesting that the trained state had no relation to orthostatic tolerance. Mangseth *et al.* (1980) tested a group of 30 subjects, including 20 runners, and found evidence suggesting a direct relationship between the number of miles run per week and the incidence of fainting during a 30-minute, 70-degree head-up tilt. The ratio was 40-50% up to 40 miles per week, increasing to 100% at 60 or more miles per week. These results suggest an impaired orthostatic tolerance with intensive aerobic conditioning. Clifford *et al.* (1981) carefully recorded the hemodynamic responses to a caudad blood-volume shift with head-up tilt in two groups of young men (20 to 29 years old) who were either untrained or endurance trained. Stroke volume and thoracic blood volume were estimated using impedance cardiography, and calf volume was measured with strain gauge plethysmography. Both at rest and during tilt, the trained subjects' heart rates were significantly lower. When normalized by the percent change in thoracic blood volume with tilt, the untrained group had larger changes in heart rate, and in mean and diastolic blood pressures than the trained group; calf volume increase was comparable in both groups. These results indicate a blunted response to blood volume shifts, and presumably to the baroreceptor stimuli that result, in trained subjects

relative to untrained ones.

Training Effects on Responses to Lower Body Negative Pressure.

The application of subatmospheric pressure to the abdomen and legs ("lower body negative pressure," LBNP), stresses the cardiovascular system similarly to head-up tilting. Musgrave *et al.* (1969) showed that, in humans, 40 mm. Hg LBNP produced a volume shift into the legs quantitatively similar to a 90-degree head-up tilt. A stress greater than that possible with a tilt table can be produced by more negative pressures; a limit of 60 to 80 mm. Hg is usually imposed by physical discomfort. In addition, head-up tilt may provoke an involuntary increase in skeletal muscle tone due to vestibular stimulation. With LBNP, the more relaxed state of the subject may unmask differences due to aerobic training that would otherwise have gone undetected.

Myhre *et al.* (1976) found that the LBNP tolerance of well-hydrated, endurance-trained runners was only 58% of that for nonrunners. This dropped to 46% with moderate thermal dehydration. They used a standard protocol of 5 minutes at each of 20, 30, 40, 50, and 60 mm. Hg LBNP, giving a maximum tolerance score of 1000 mmHg-minutes. The trained group had a larger relative increase in leg volume, which, the authors concluded, reflected a larger

overall shift in body fluids, contributing to their lower LBNP tolerance. Luft (1980) compared long distance runners with nonathletes, swimmers, and weightlifters using the same LBNP protocol. Very few differences in resting or LBNP-stressed parameters were found between the swimmers, weightlifters and nonathletes, so for some comparisons they were pooled to provide a group of nonrunners to contrast with the runners. The runners had the highest maximum oxygen uptake, the highest leg compliance, and the lowest LBNP tolerance, of all the groups. There were no differences in resting or maximal heart rates, in the percent of increase in heart rate or leg volume, or in post-LBNP residual leg volume (reflective of fluid filtration).

Paynter *et al.* (1977) compared the blood pressure responses of untrained and endurance trained rats to a protocol of step-increasing LBNP. (For rats, the maximum usable negative pressure is 10 mm. Hg.) After a twelve week program of treadmill running, the trained rats had significantly lower blood pressures at each level of LBNP tested. Tipton *et al.* repeated the experiment, and found that, at 5 mm. Hg LBNP, the untrained animals' pressures fell an average of only 5%, while those of the trained animals dropped by 20%. At 10 mm. Hg LBNP, these values became 36% and 42%, resp., and they were significantly different.

The LBNP data illuminate the differences between

sedentary and trained subjects, whereas the tilt-table data are less definitive. This may be due to the greater stress possible with LBNP, since head-up tilting would not have revealed the LBNP intolerance of the runners: in Luft's study (1980), only two of the 13 failed to reach the equivalent level (40 mm. Hg) of negative pressure.

Training Effects on Responses to Centrifugal Acceleration.

Headward acceleration (blood shifted out of the head and thorax, into the abdomen and legs) on a human centrifuge can provoke larger cardiovascular responses than are possible with tilting and LBNP. Several attempts have been made to differentiate well-trained from sedentary individuals based on their "relaxed" acceleration tolerances. Cooper and Leverett (1966) found no difference between nonrunners and runners who had been training for 3 1/2 months, in response to either a gradual-onset (0.07 G/sec.) or a rapid-onset (1 G/sec.) acceleration protocol. This finding was confirmed by Klein *et al.* (1969a,b), using the same acceleration protocols. Runners lost their central vision (indicating retinal ischemia due to inadequate eye-level blood pressure) at 6.8 G, and nonrunners, at 6.9 G, on gradual-onset centrifuge runs. Both groups reached nearly 5 G on rapid-onset runs. Having determined from these and other studies that relaxed acceleration tolerance is unaffected by aerobic conditioning, Epperson

et al. (1982) investigated the usefulness of running and weight-training in augmenting straining acceleration tolerance. Straining, by contraction of the skeletal muscles to reduce venous volume and enhance venous return, and by forceful expiration against a partially-closed glottis to augment ventricular emptying, increases acceleration tolerance (Burton et al., 1974). The centrifuge protocol consisted of simulated aerial combat maneuvering, alternating 15-second plateaus of 4.5 and 7 G continuously, until the subject's voluntary endpoint of fatigue was reached. Three groups of subjects underwent 12 weeks of weight training, running, or no regular exercise. Only the runners showed an increased maximum oxygen uptake and an increased blood volume. The weightlifters increased their straining acceleration tolerance, but there were no such changes with the runners and the controls.

As discussed above, neither the centrifuge nor the tilt table protocols seem to differentiate between sedentary and endurance-trained individuals' resistance to orthostatic stresses to the extent that LBNP studies do. The tilt tests are apparently not stressful enough to invoke those cardiovascular regulatory mechanisms affected by endurance training (although impending syncope would seem to be a sufficient stress). The centrifuge stress may overwhelm those regulatory mechanisms. The combination of an intermediate stress and a relaxed state, as provided by LBNP, seems required.

Training Effects on the Arterial Baroreceptor Reflexes.

Of the studies which have revealed differences in the response to orthostatic stress due to the trained state, several implicate changes in the arterial baroreceptor reflexes. Tipton *et al.* (1982) compared the cardiovascular responses of untrained and treadmill-trained rats, at rest, to LBNP, both before and after sino-aortic baroreceptor denervation. At 5 and 10 mm. Hg of LBNP, baroreceptor denervation significantly reduced the ability of the untrained rats to maintain blood pressure during LBNP, but had no such effect on the trained group. There were no differences between the groups after denervation, at any level of LBNP. Tipton *et al.* concluded from this that the baroreflex is largely unresponsive in trained rats, there being no effect of baroreceptor denervation on the fall in blood pressure during LBNP. However, there was a significant effect of denervation on the untrained animals. Stimulating the carotid sinus baroreceptors by altering carotid sinus transmural pressure with neck suction has been used to address this question in man. Stegemann *et al.* (1974) and Clifford *et al.* (1981) observed reduced heart rate and blood pressure responses to carotid sinus stimulation in endurance trained young men at rest.

Analysis of Dynamic Response Characteristics: The Frequency Domain.

No matter what the intensity of the chosen stress, each method described thus far sought to determine only the conditions necessary for the "collapse" of circulatory function. Most employ static, or slowly changing, stresses. Even the centrifuge protocol of Epperson *et al.* (1982) used a rapidly-changing acceleration to reach the same endpoint, circulatory collapse. However, the pattern of response to these stresses contains information which may be lost if not specifically examined.

Some of this otherwise lost information can be quantified by the analysis of the dynamic response characteristics of the system. Such analyses have been applied to problems in vestibular physiology (Buettner *et al.*, 1981), gas exchange (Daubenspeck, 1973), and cardiopulmonary adjustments to acute exercise (Chang and Snellen, 1982). There is a rich literature of their use in investigating the components of cardiovascular regulation. A common technique is to perturb the intact system repetitively by sinusoidally varying blood pressure or flow, and measuring the systemic response at different frequencies of the repetition. Alternatively, the dynamic stress can consist of a "random" or "noise" input of pressure or flow: the input is actually the sum of sine waves of many frequencies. Signal processing techniques determine the

response amplitude at each of the input frequencies. The contributions of the various effectors can be assessed by selectively eliminating them, either surgically or pharmacologically, and observing the differences in systemic functioning in their absence. (Note that this approach assumes there are no compensatory changes in the remaining systems.) Carrying this approach even further, isolated organ systems and vascular beds can be perturbed, to determine their individual dynamic response characteristics. At this level, the input may be variations in pressures or flows, or may take the form of efferent nerve stimuli following a sinusoidal or random pattern. These analyses have revealed facets of circulatory regulation that would have gone unnoticed with other techniques.

The circulatory response to these stimuli usually follows a well-defined pattern. Adequate regulation at low frequencies gives way to increasingly less efficiency in minimizing the disturbance, until the variations reach a maximum at an intermediate frequency. Thereafter, due to the structural characteristics of the vascular bed, the amplitude of the oscillations falls off with increasing frequency of perturbation. This pattern can be understood in terms of the steps that the control system follows during the regulation process.

There is a finite time required for a perturbation to be sensed and then acted upon. If subsequent perturbations occur at longer intervals than this response time,

adequate regulation can be maintained. If the disturbances occur more frequently, regulation is impaired. Variations in the regulated parameter reach a maximum at that frequency for which the effectors are responding exactly out of phase with the actual disturbance. At this "resonant frequency," the effectors' actions are now just the opposite of the appropriate ones. The resonant frequencies for various organ systems are usually between 0.02 and 0.06 Hz (see: Tables I-III), so these systems best minimize disturbances which have periodicities of at least 15 to 50 seconds.

A useful analogy to the frequency response characteristics of an organ or organ system can be found in spectroscopy. The nature of a chemical specimen's covalent bonds can be determined by exposing the specimen to a range of electromagnetic radiation and determining at which wavelength it re-radiates the absorbed energy. Similarly, the responsiveness of a vascular bed can be determined by the frequency of blood pressure or flow oscillations to which the vascular bed responds most strongly.

Cardiovascular Frequency Response Characteristics.

The responses of the intact organism to phasic systemic inputs have been examined in only a few laboratories. Guyton *et al.* (1951) employed repetitive hemorrhage and reinfusion of 10% of the blood volume to induce blood

pressure oscillations in dogs. A wide range of frequencies were examined under two protocols: either the total volume shifted remained constant, or the flow rate was maintained. Both types of experiments revealed a change in the amplitudes of the pressure oscillations at about 0.03 Hz. When the volume shifted was constant, pressure oscillations were minimized at the lower frequencies, and increased above 0.03 Hz. The cardiovascular system was capable of reducing the impact of the slow blood volume changes, but couldn't respond quickly enough to compensate for the faster ones. When a constant rate of volume inflow and outflow was maintained, pressure oscillations were lower at frequencies above 0.035 Hz. In this case, much more blood volume was exchanged during the low frequencies, since there were longer periods over which volume could be infused or withdrawn. The large excursions in blood pressure reflect the large volumes exchanged. Brown and Taylor (1972), using the constant-volume technique, confirmed these observations, and found that in the sino-aortic denervated preparation, the aortic pressure oscillations decreased passively with increasing frequency, from 113 mm. Hg at 0.002 Hz to 18 mm. Hg at 0.067 Hz. These data are believed to reflect whole-body autoregulation.

Taylor (1966) induced oscillations in the aortic flow of dogs by randomly exciting the sino-atrial node, and spectrally analyzed the resulting aortic pressure-to-flow

(impedance) relationships. He found a maximal response at 0.035 Hz, indicating that the poorest regulation of pressure occurred at around this frequency. This maximum disappeared after ganglionic blockade with hexamethonium. These results suggest that the arterial baroreflexes regulate peripheral resistance most effectively up to about 0.015 Hz. Due to the delays inherent in the reflexes, they exacerbate the situation at frequencies up through about 0.035 Hz. Beyond 0.035 Hz, the disturbances are damped out passively, forestalling any baroreflex contribution.

Regulation of arterial pressure responses to centrifugally-produced whole-body forcing inputs was examined by Gillingham *et al.* (1977) in man. Applying spectral analysis to the eye-level blood pressure responses of three subjects to simulated aerial combat maneuvering, they found a maximal pressure response of 35 mm. Hg at 0.06 Hz, decreasing to 15-20 mm. Hg at lower (less than 0.01 Hz) and higher (greater than 0.10 Hz) frequencies. Marquis (1978) and Knapp *et al.* (1982) used a sinusoidally-varying 2G vector along the animal's spinal axis, with the dog in several states of autonomic reflexiveness. Knapp *et al.* found a maximum pressure variation of about 45 mm. Hg between 0.032 and 0.052 Hz, of which Marquis determined 26 mm. Hg to be amplitude of the first harmonic component.

Mechanistic explanations for these response patterns have been sought using isolated organ preparations. A

common technique involves sinusoidal pressure changes to stimulate the arterial baroreceptors, usually in the isolated carotid sinus, and recording the blood pressure responses of the vascular bed. The measured gains (response amplitude/stimulus amplitude; Table I) vary from study to study by a factor of 4 to 5, depending on stimulus magnitudes and the state of the animal preparation. However, the resonant ("corner") frequencies are remarkably uniform, lying mostly between 0.02 and 0.03 Hz, and dropping to less than 0.01 Hz with vagotomy. Thus, one would expect the carotid sinus baroreceptors to be most effective in minimizing pressure disturbances at least 33-50 seconds apart. Arterial pressure, the variable normally regarded as being regulated, is determined by heart rate, stroke volume, total peripheral resistance, and central venous pressure. The problem now becomes one of determining the contributions of each of these in the minimization of pressure disturbances.

The frequency behavior of central venous pressure has not been examined, but Marquis (1978) evaluated diastolic right ventricular pressure in his study. He reported almost no change in mean diastolic RVP from 0.009 to 0.25 Hz. The amplitudes of diastolic RVP oscillations remained roughly constant at 5-7 mm. Hg up to about 0.10 Hz, and then increased to about 8-10 mm. Hg at 0.25 Hz. These oscillations were about 180 degrees out of phase with the acceleration input, indicating a passive response to vol-

TABLE I: ARTERIAL BARORECEPTOR REFLEX CHARACTERISTICS

<u>Baroreceptor</u>	<u>Author(s) & Date</u>	<u>Gain</u>	<u>Corner Freq. (Hz.)</u>	<u>Comments</u>
carotid sinus	Scher & Young (1963)	2.5 - 10 2.0 - 6	0.02 - 0.03	cats dogs
	Grodins (1963)	3.9	0.017	vagotomized dog
	Levison et al. (1966)	2.0 - 4.4	0.03 - 0.04	dogs
	Hatakeyama (1967)	0.6	0.017	rabbits: right carotid sinus & aortic arch denervated; above + vagotomy
	Kenner (1971)	0.9 1.5 - 3.5 2.5 - 4.6	0.008 0.03 < 0.01	a dog (?) above + vagotomy
aortic arch	Scher et al. (1967)	--	0.015 - 0.032	4 dogs
	Ito (1969)	--	0.02	2 dogs
	Lloyd (1973)	0.8 - 2.5	0.03 - 0.05	5 dogs: varied left atrial pressure
	Allison (1968)	--	0.016 - 0.033	dogs: isolated aortic arch

ume shifting. Central venous pressure should reflect, among other things, the responses of peripheral venous beds to the forcing input. Penaz (1963) observed a purely passive response in the capacitance vessels of the rabbit ear to sinusoidal nerve stimulation. Thus, there seems to be little active control of the venous system at the frequencies studied.

Heart rate responses to several types of time-varying inputs are summarized in Table II. These results show the heart rate component to have a resonant or corner frequency somewhat higher than the carotid sinus baroreceptors, although there is a large variation between reports. For instance, Scher *et al.* (1972) found a corner frequency of 0.15 Hz in dogs and baboons, while Stephenson *et al.* (1981), working in the same laboratory and using the same techniques, present evidence suggesting it is no higher than 0.032 Hz. Most other reports fall between those extremes (Table II).

Stroke volume should be susceptible to the frequency-dependent characteristics of the venous side of the circulation, since it is dependent on right ventricular filling. Sagawa (1967) varied arterial and left atrial pressures, individually, in a sinusoidal manner, and found that, in both cases, the ratios of the amplitudes of stroke volume to arterial pressure oscillations increased linearly with frequency. The corner frequency was greater than 0.10 Hz when the means of both pressures were sub-

TABLE II: HEART RATE RESPONSES TO SINUSOIDAL STIMULATION

<u>Author(s) & Date</u>	<u>Stimulus</u>	<u>Corner Freq. (Hz)</u>	<u>Comments</u>
Penaz (1962)	nerve stimulation	0.09	rabbit; sinusoidally-modulated vagal stim.
Chessa & Calaresu (1971)	"	0.031 - 0.054	3 cats; sinusoidally-modulated vagal stim.
Hatakeyama (1967)	baroreflex	0.033	rabbits; carotid sinus pressure oscillations.
Lim & Fletcher (1968)	"	0.08 - 0.10	humans; 360 degree pitch rotation.
Hamilton et al. (1969)	"	0.04 - 0.06 0.017	humans, normal; humans, quadriplegic; sinusoidal 24 degree head-up tilt.
Scher et al. (1972)	"	0.15	dog, baboon; sinusoidal inflation of cuffs on ascending and descending aorta.
Marquis (1978)	"	0.04 - 0.06	dogs; sinusoidal \pm 2 Gz.
Stephenson et al. (1981)	"	below 0.032	5 baboons; sinusoidal inflation of cuffs on ascending and descending aorta.
Knapp et al. (1982)	"	0.032 - 0.052	dogs; sinusoidal \pm 2 Gz.

physiological, and much lower (0.03-0.04 Hz) when either was above normal. Knapp *et al.* (1982) found a decrease in stroke volume oscillations with increasing frequency from 0.008 to 0.25 Hz, which if divided by arterial pressure oscillations, indicates a break at 0.032-0.052 Hz and a leveling off thereafter. Marquis (1978) noted a maximum in the amplitude of the first harmonic of stroke volume excursions at about 0.04 Hz, with a rapid decrease at higher frequencies. There are some basic differences in the stroke volume responses to sinusoidal stimulation between these studies. Sagawa (1972) directly varied only preload and/or afterload, while Marquis (1978) and Knapp *et al.* (1982) observed the SV responses to global shifts in blood volume. However, these studies all indicate a change in the response characteristics of stroke volume at about 0.03-0.05 Hz. Marquis' analysis of the stroke volume phase angles supports the contention that its response to sinusoidal forcing is passive, reflecting venous return and afterload changes, rather than being actively controlled by neural mechanisms.

Cardiac output responses to sinusoidally-varying carotid sinus pressures (Paris *et al.*, 1981) and to oscillatory acceleration (Marquis, 1978; Knapp *et al.*, 1982) have been shown to remain constant across the frequency spectrum. Any variations are the result of changes in heart rate and stroke volume, and neural control was limited to the heart rate component.

Total peripheral resistance, and the resistances of the individual vascular beds, clearly show frequency-dependent responses (Table III). Stegemann and Geisen (1966) varied carotid sinus pressure sinusoidally in a dog preparation with all other baroreceptors denervated, and found that the TPR oscillations remained constant in amplitude up to a stimulus frequency of 0.02 Hz, beyond which they fell off sharply. Using flow disturbances generated by random pacing of the SA node, Taylor (1966) found a corner frequency of 0.035 Hz. Marquis (1978) found the same pattern in the amplitudes of the first harmonics of systemic resistance, which increased by 50% between 0.008 and 0.04 Hz, and then fell sharply with increasing frequency. The amplitudes reported by Knapp *et al.* (1982) were slightly larger than those of Marquis, but showed only a steady decrease with increasing frequency.

Resistance responses to phasic inputs have been reported for several different vascular beds (Table III). Most of these studies revealed resistance oscillations of constant amplitude up to some corner frequency, with a rapid attenuation in amplitude thereafter. The corner frequency for skeletal muscle, coronary, and cerebral vascular beds is about 0.02-0.03 Hz. For the splanchnic and renal beds, it is usually below 0.01 Hz. Thus, there appears to be a functional difference between the vascular beds: changes in the splanchnic vasculature are limited to periods below about 1.5-2 minutes, and the skeletal muscu-

Table III: PERIPHERAL RESISTANCE RESPONSES TO
SINUSOIDALLY OSCILLATING STIMULATION

Vascular Bed	Animal Prep.	Oscill. Stimulus	Corner Freq. (Hz)	Author(s)	Date
Total peripheral resistance	dog	carotid sinus press.	0.02	Stegemann & Geisen	1966
	dog (n=11)	SA node stim.	0.035	Taylor	1966
	dog (n=5)	± 2 Gz	0.04	Marquis	1978
	dog (n=10)	"	0.032-0.052	Knapp et al.	1982
cerebral	rabbit (n=12)	cervical sympath.	0.03-0.04	Penaz & Burianek	1963
coronary	rat	perfusion pressure	0.02	Basar et al.	1968b
skeletal muscle (hind qtrs.)	rabbit	lumbar sympath. nerve	0.04-0.06	Penaz et al.	1966
	dog (n=16)	"	0.017	Rosenbaum & Race	1968
	dog	perfusion pressure	0.02-0.03	Kenner et al.	1971
	baboon (n=4)	"	0.02	Spelman & Pinter	1978
visceral:					
kidney	rat	perfusion pressure	0.02	Basar et al.	1968
	rat	"	0.007-0.03	Basar & Weiss	1968
	dog	"	0.005	Kenner & Ono	1971

	dog	"	0.008	Kenner et al.	1975
splanchnic	cat (n=3)	splanchnic nerve	<0.01	Scher & Young	1963
	cat	"	0.03- 0.04	Penaz et al.	1966
	dog	perfusion pressure	0.005	Kenner & Ono	1971
	dog	"	0.007- 0.008	Kenner et al.	1975

taenia coli	guinea pig	stretch	0.03- 0.04	Golenhofen	1964

lature is involved in changes as fast as about 30 seconds apart. This pattern has been attributed to the passive damping of the induced pressure disturbance at frequencies above the corner frequency. However, the pattern is also found in experiments using sinusoidally modulated nerve stimulation to alter the resistance to a constant perfusion pressure, in which passive damping should not be involved. One might speculate that the neural pattern is, in effect, "tailored" to the hydraulic characteristics of the vascular bed. As a result, since the vasculature seldom experiences the higher-frequency pressure oscillations, the nervous system does not have the capability to respond at those frequencies.

The fundamental reason for the observed pattern in the frequency responses of the peripheral vasculature may reside at an even lower level of organization: the smooth muscle itself. In a simple experiment, Golenhofen (1964) applied sinusoidal stretches of different frequencies to the taenia coli of the guinea pig, and measured the tension developed at each frequency. The taenia coli is a visceral smooth muscle often used in such work. Both the mean tension developed and the amplitude of the oscillations in tension remained constant up to 0.03-0.04 Hz, fell to their minima at 0.2 Hz, rose to a secondary peak at 0.5-0.7 Hz, and then declined at still higher frequencies. The agreement between Golenhoffen's results and the resistance curves determined for the cerebral, coronary,

visceral, and renal vasculature leaves little doubt that vascular smooth muscle is a major determinant of local frequency response characteristics. In turn, these vascular beds shape the TPR contribution to the systemic arterial pressure response.

Perhaps the least explored area of cardiovascular frequency dependency is the role of circulating, neuro-humoral agents: catecholamines, vasopressin, and the renin-angiotensin system. Being blood-borne, their response times are long, so they are of necessity more involved in the chronic regulation of arterial pressure than in acute changes. The catecholamine norepinephrine enters the plasma primarily by leaking from sympathetic nerve endings. Its plasma clearance in adult man is about 1.5 l/min. (Christensen and Galbo, 1983). For a 20 kg. dog, with an assumed blood volume of 1.5 l and a maximal sympathetic activation time of 20 seconds (Scher and Young, 1963), a complete cycle of norepinephrine appearance and disappearance would take about 80 seconds. This is comparable to a periodicity with a frequency of about 0.01 Hz, which would be norepinephrine's hypothetical corner frequency. The plasma catecholamine epinephrine is released by sympathetic stimulation of the adrenal medulla. At an infusion rate of 10 ug/minute, it takes about 3 minutes to have its maximum effect on blood pressure in man, and the effects disappear in about 5 minutes when the infusion is discontinued (Allwood *et al.*, 1963). If the

in *vitro* rates are comparable to those following release in *vivo*, epinephrine has the potential for periodicities at frequencies below 0.002 Hz. In the definitive study of the vasopressin arterial pressure control system in the dog, Cowley *et al.* (1980) observed a maximum response time to hemorrhage in the decapitated dog of less than 5 minutes, and a decay half-life of 3.5 minutes. The renin-angiotensin system responds maximally over a period of approximately 15 minutes (Cowley *et al.*, 1971). Thus, the sympathetic nervous system would exert its influence up to about 0.05 Hz, circulating norepinephrine up to 0.01 Hz, vasopressin up to 0.003 Hz, epinephrine up to 0.002 Hz, and renin-angiotensin below 0.001 Hz. It should be noted, however, that the influence of a humoral factor is not limited to the frequency regime determined by its rate of appearance and disappearance. The renin-angiotensin system has been shown to influence the amplitude of spontaneous heart rate oscillations at around 0.04 Hz, a period of about 25 seconds (Akselrod *et al.*, 1981). This probably occurs by effecting some long-term change on the periphery which is reflected in heart rate variability.

As determined by their frequency response characteristics, the components of blood pressure regulation seem to operate in the following ranges: the humoral factors are important up to about 0.005 Hz; neural control of the visceral vasculature falls off above 0.01 Hz, while that of the skeletal muscle vasculature extends to 0.04 Hz;

cardiac mechanisms, especially heart rate, function best between 0.02 and 0.1 Hz; and, at higher frequencies, passive damping eliminates the need for active control (Taylor, 1966; Hatakeyama, 1967; Marquis, 1978; Knapp *et al.*, 1982). A comparison of the frequency response characteristics of untrained and endurance trained subjects should indicate which components of the cardiovascular control system are changed by the frequency range in which the difference occurs.

Statement of the Problem.

The purpose of this dissertation was to test the hypothesis that endurance training alters the frequency response characteristics of the cardiovascular system. This was accomplished by comparing the circulatory responses of untrained and endurance trained dogs to oscillatory blood volume shifts produced by sinusoidal acceleration. The level of acceleration, 2 G, provided a sufficient stress to elicit a systemic response above baseline levels, but did not threaten to collapse the circulatory system. Chronic instrumentation of the animals permitted measurement of the cardiac and vascular components of blood pressure regulation. Sedating the animals without inducing anesthesia allowed the measurements to reflect the intact, integrated capabilities of the cardiovascular system. As a result, this effort produced a quantitative

distinction between the dynamic response characteristics of two well-defined states: normal (sedentary) and aerobically endurance conditioned.

METHODS

Male mongrel dogs weighing between 15 and 25 kg. were used as experimental subjects. Initial resting and exercise heart rates were determined for each animal, which was then randomly assigned to one of two groups. The "untrained" group immediately underwent surgery for chronic instrumentation. The "trained" group was first aerobically conditioned with six weeks of treadmill running. After training was completed, their resting and exercise heart rates were again measured. The trained group underwent surgery for chronic instrumentation. After post-operative recovery, and supplemental conditioning of the trained group, final measurements of resting and exercise heart rates were taken.

On the day of the centrifuge experiment, acute physiological instrumentation was implaced, and the dog was restrained on the animal platform of the centrifuge. The animal then experienced a set of input acceleration frequencies between 0.008 and 0.25 Hz.

Animal Care and Handling.

All animals were housed in facilities at the Wenner-Gren Research Laboratory, in pens measuring 93 x 185 cm.

Lighting was on a 14L:10D schedule, and temperature was maintained at about 20 degrees C. Animals were allowed daily access to an enclosed run open to the outside. They were fed (Purina Dog Chow) daily following training sessions, and were watered ad libitum. Body weights were checked weekly during training and post-operative recovery. The principles of laboratory care as outlined by the National Society for Medical Research were rigorously adhered to.

Pretraining, Post-training, and Post-surgery Measurements.

After familiarization with treadmill running, all animals' resting and exercise heart rates were measured. The procedure was repeated with the trained group at the end of training, and with all animals approximately 2 1/2 weeks after implant surgery. Heart rates were used to quantify the degree of cardiovascular conditioning, and the differences in the trained states of the two groups at set times during the project. No other attempts to quantify these differences were made, since Ordway *et al.* (1982) showed that an identical training program produced significant increases in gastrocnemius citrate synthase activity, an objective determinant of skeletal muscle conditioning.

Resting heart rate determinations were made with the dog in a transport cage (84 x 70 x 77 cm) placed in a

quiet, lighted room. Three surface electrodes on the chest allowed recording of the electrocardiogram and triggering of a cardiometer, both displayed on a Beckman two-channel strip-chart recorder. After a thirty-minute adjustment period following isolation, the six lowest one-minute heart rate counts during the next 15 minutes were determined. The lowest heart rate of the six was discarded, and the remaining five were averaged to give the dog's resting heart rate.

Exercise heart rates were determined during a standardized multi-stage exercise test (Tipton *et al.*, 1974). This test consisted of seven 3-minute periods of progressively-increasing intensity exercise on the treadmill: standing quietly on the treadmill; 3 miles (4.8 km) per hour at 0% inclination; and, 4 miles (6.4 km) per hour at 0%, 4%, 8%, 12%, 16%, and 20% inclination. Electrocardiogram and cardiometer were recorded as during resting measurements, with heart rates being determined during the last 45 seconds of each 3-minute stage. Recovery measurements were made at one, three, and six minutes post-exercise.

Training Program.

The physical training program employed was based on one described by Wyatt and Mitchell (1974). The dogs ran on a motor-driven treadmill (Quinton model 1849c) at

speeds of 4-6 miles per hour (6.4-9.6 kilometers per hour) at a 10% incline for one hour daily, five days per week, for six weeks. During the first week, exercise duration was progressively increased from 30 minutes to the maximum of one hour. All dogs ran freely and were either untethered or had a rope placed loosely around the neck.

Heart rates were monitored periodically during training, and treadmill speeds were adjusted to elicit a rate of 180-200 beats per minute during the hour-long sessions. Room temperature was maintained at approximately 18-21 degrees C.

At least 24 hours elapsed between a training session and any measurement of resting or exercise heart rate.

Surgical Procedures for Chronic Instrumentation.

Before surgery, each dog was anesthetized with sodium pentobarbital (Veterinary Laboratories, Inc., 20 mg/kg) administered intravenously. They were intubated and placed on positive-pressure respiration. Using sterile technique, a left thoracotomy was performed through the fourth intercostal space. The heart was then exposed by cutting the pericardium longitudinally and constructing a pericardial cradle. The heart was reflected, and a pressure transducer (Konigsberg Instruments, model P19) was placed in the left ventricle through a stab incision in the apical dimple, and secured by a purse-string suture.

With the heart in the pericardial cradle, a section of the ascending aorta near the base of the heart was carefully cleaned of connecting tissue. A strip of dacron mesh was wrapped loosely around the cleaned aorta, and an electromagnetic flow probe (Zepeda Instruments) was placed around the mesh. (The mesh served to enhance scar tissue growth and thus reinforce the aorta against rupture due to the relative motion of the flow probe.) The connecting leads from the chronic instrumentation exited the thorax at the third intercostal space, and were stored in a subcutaneous pouch placed between the scapulae (McCutcheon *et al.*, 1982). The chest was then closed, and the dog placed in the recovery kennel for several hours. Analgesics and antibiotics were administered as needed during post-operative recovery.

Experimental Animal Preparation.

On the day of the centrifuge experiment, the dog was sedated with an intramuscular injection of an analgesic-tranquilizer, Innovar-Vet (fentanyl (Sublimaze), 0.05 mg/kg, and droperidol (Inapsine), 2.5 mg/kg; Pitman-Moore). Supplemental doses (0.5 ml/20 kg) of Innovar-Vet or of fentanyl were administered intravenously every hour to maintain the lightly-tranquilized state. This sedative was chosen to minimize the startle response of the animal while preserving the reflex capability of the cardiovascu-

lar system (Buckhold et al., 1977).

Under local anesthesia (4% Lidocaine; Invenex), a multilumen catheter (Swan-Ganz, 7 French) was inserted into a branch of the femoral vein, advanced under fluoroscopy through the venous system into the pulmonary artery. Using this catheter, cardiac output was determined by the thermal dilution method, using cold saline and a cardiac output computer (Waters Instruments Co., model TC-1). These determinations permitted the calibration of the implanted electromagnetic flow probe. Then, to minimize clot formation, this catheter was replaced with another (Cutter Laboratories, Inc., feeding tube, 8 French) for drug infusions. Piezo-electric manometer-tipped catheters (Millar PC-350, 5 French) were placed, under local anesthesia, in the right and left ventricles via small branches of a femoral vein and artery, respectively. The left ventricular Millar catheter was used to calibrate the implanted Konigsberg transducer, then was retracted to a point just outside the aortic valve to measure aortic pressure. The other Millar was left in place to measure right ventricular pressure.

Centrifuge Facility.

Low-frequency blood volume shifts were produced by sinusoidal acceleration loadings generated by a modified 50-foot (15.24 m) diameter centrifuge (Figure 1A). A



Figure 1A. Fifty foot diameter centrifuge with platform.

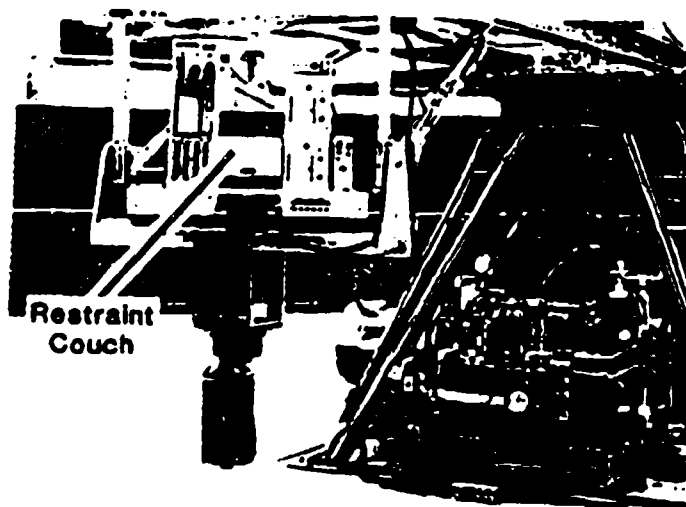


Figure 1B. Close-up of platform and end view of animal restraint couch.

platform (Figure 1B), which could be independently counter-rotated, was mounted to the large arm of the centrifuge. The supine animal was restrained on the platform, with its center of rotation approximately at heart level. With the large centrifuge arm rotating at a speed producing a radial 2 G acceleration (that is, twice earth's surface gravity), constant counter-rotation of the animal platform resulted in the desired sinusoidal acceleration along the animal's spinal axis. (Acceleration along the spinal axis is termed "Gz," and "+Gz" and "-Gz" produce caudal and cephalad blood volume shifts, respectively. A "Gy" acceleration acts from one side of the animal to the other.) A Gy component 90 degrees out of phase with the Gz is also produced. The platform rotation speed determined the frequency of the sinusoidal input acceleration, such that, for example, one rotation every 125 seconds produced an input frequency of 0.008 Hz.

Acceleration Protocol.

All indwelling instrumentation was connected and calibrated, and the animal secured in the restraint couch. The couch was mounted on the platform, and all variables allowed to stabilize. Following a preacceleration control period, the test series of sinusoidal accelerations was conducted. These were $\pm 2Gz$ inputs at ten discrete frequencies, ranging from 0.008 Hz (125 seconds per cycle) to

0.23 Hz (4 1/3 seconds per cycle).

Peak-to-peak acceleration of 4 G was chosen to stress the animal to a greater extent than occurs normally, but not so much as to produce circulatory collapse. This level of acceleration also generates intravascular pressure variations quantitatively similar to invasively-applied stimuli used by other investigators (Scher *et al.*, 1967).

The acceleration frequencies were applied sequentially from lowest to highest, without stopping, allowing 5-6 minutes per test frequency at the lowest frequencies and 2-3 minutes at the highest. Previous work (Knapp *et al.*, 1982) has shown that this continuous protocol minimized the time required for a stable response to develop at each frequency. The order of presentation (highest-to-lowest ~~vs.~~ lowest-to-highest; sequential vs. random) has been shown to have no affect on the response (Marquis, 1978). At the end of an experiment, the animal was sacrificed using a lethal dose of sodium pentobarbital.

Data Acquisition and Analysis.

A continuous on-line magnetic tape record (Ampex FR-3020, 14-channel recorder) and a strip-chart record (Beckman type RM dynograph) were made of the analog variables: aortic pressure (AP) and flow (AF), left and right ventricular pressure (LVP, RVP), and spinal axis accelera-

tion. Heart rate was determined from the time between successive threshold-crossings of LVP. An on-line computer (Raytheon 704) calculated stroke volume (SV), cardiac output (CO), and the ratio of (AP minus diastolic RVP) divided by CO. This served as an estimate of total peripheral resistance (TPR). Coronary blood flow was not included in the calculation. These digital variables were displayed on another polygraph beat-by-beat, one-beat-delayed.

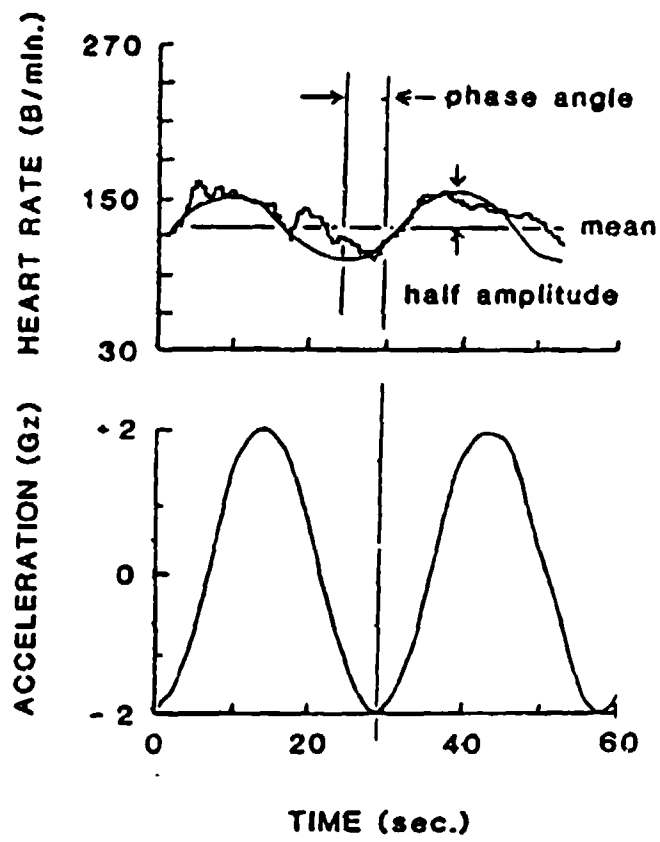
During off-line processing, a computer (Digital Equipment Corp., PDP11/34) recalculated the digital variables from the analog signals on tape, averaged over each beat without imposing the one-beat delay. Only the diastolic portions of the right and left ventricular pressures were analyzed. A computer program determined diastole from threshold crossings of left ventricular pressure, ignored the left and right ventricular systolic pressures, and substituted linearly interpolated values for each measurement during systole. Since even the highest input acceleration frequencies were still much lower than the lowest heart rate, this procedure provided a valid "analog" diastolic pressure signal. All analog and digital variables were then sampled at 6.2 msec intervals, and processed through a 1-Hz, low-pass Hanning filter. The filtered signal was compressed by choosing every n -th point ($n = 8$ to 15, depending on test frequency and record length). A Fast Fourier Transform (FFT) program processed

all variables. This program provided the mean value of the variable during each frequency exposure, and the amplitude and phase angle of the first harmonic component of the filtered signal (Fig. 2). These values were analyzed, rather than the corresponding "by hand" determinations, for several reasons. Fourier analysis is a standard analytical method of describing and evaluating system dynamics where the time-dependent responses of the variables of interest to a sinusoidal forcing function can be experimentally measured. It eliminates the variability and bias inherent in human interpretation of the data. Finally, in addition to amplitude information, it provides the time relationship (phase lead or lag) of the first harmonic components of the output variables with respect to each other and to that of the input function.

All comparisons of mean values, amplitudes and phase angles between the groups were tested for statistical significance using a two-factor, mixed-design analysis of variance. Where indicated by the ANOVA, the differences between group means at specific frequencies were subjected to the Newman-Keuls Multiple Range Test. In all cases, a probability of chance occurrence of 0.05 was taken as statistically significant.

All data are presented as group means, and standard errors of the means, for each input acceleration frequency. Statistical significance is indicated where appropriate. Additionally, the amplitudes and phase angles of

Figure 2. Illustration of the result of a Fast Fourier Transform: a sample of the instantaneous heart rate response to sinusoidal acceleration, and its mean value and the amplitude and phase angle of the harmonic component, as determined by FFT.



selected variables were plotted over a range of relative frequency inputs. This analysis used the maximum amplitude of the first harmonic of heart rate to specify each animal's "resonant" frequency. The other input frequencies for that animal were then expressed as fractions of this resonant HR frequency. The data corresponding to these normalized frequencies were collected in bins, with the bin "floors" being: 16%, 35%, 55%, 75%, 99%, 101%, 150%, and 275% of the resonant HR frequency. Each animal is represented at least once, but as few times as possible, in each bin; multiple values for a dog in a bin were averaged. This format eliminated much intra-group variability and provided a clear picture of the frequency responses of the cardiovascular variables as they relate to the heart rate data.

RESULTS

This chapter presents the analyses of comparisons between untrained and endurance trained dogs. Resting and exercise heart rates are discussed first, followed by the responses of both groups of animals to the acceleration stress.

Resting and Exercise Heart Rates.

The heart rates for the two groups of animals at rest and during several levels of submaximal exercise, before any training other than treadmill familiarization, are graphed in Figure 3. There are no heart rate differences between the groups at rest, at any intensity of exercise, or during recovery from exercise.

Heart rates for seven dogs before and after endurance training are presented in Figure 4. There was only a slight reduction in resting heart rate with training, but a significant reduction at the higher exercise intensities [4 miles (6.4 kilometers) per hour at 4 percent or more inclination] and in the first minute of recovery.

The heart rate measurements made 18 days after implant surgery are shown in Figure 5. Again, there was no

Figure 3. Comparison of the heart rate responses of all the dogs to submaximal exercise test, before the trained group began its training program. Open circles are means of untrained dogs (sedentary controls), closed circles are means of trained dogs (before training), and bars indicate standard error of the mean.

HEART RATE RESPONSES TO SMT BEFORE TRAINING

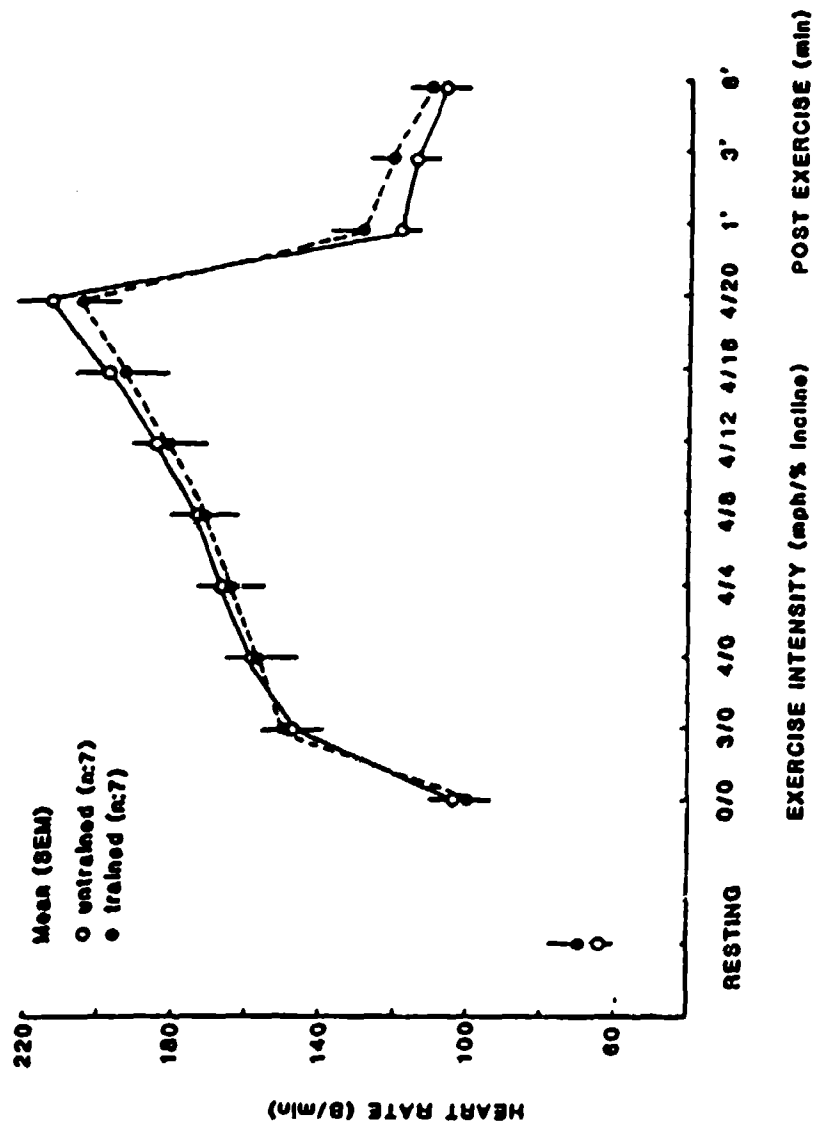


Figure 4. Comparison of heart rate responses to a submaximal exercise test of the "trained" dogs, before and after training. Symbols as in Figure 3.

HEART RATE RESPONSES TO SMT BEFORE AND AFTER TRAINING

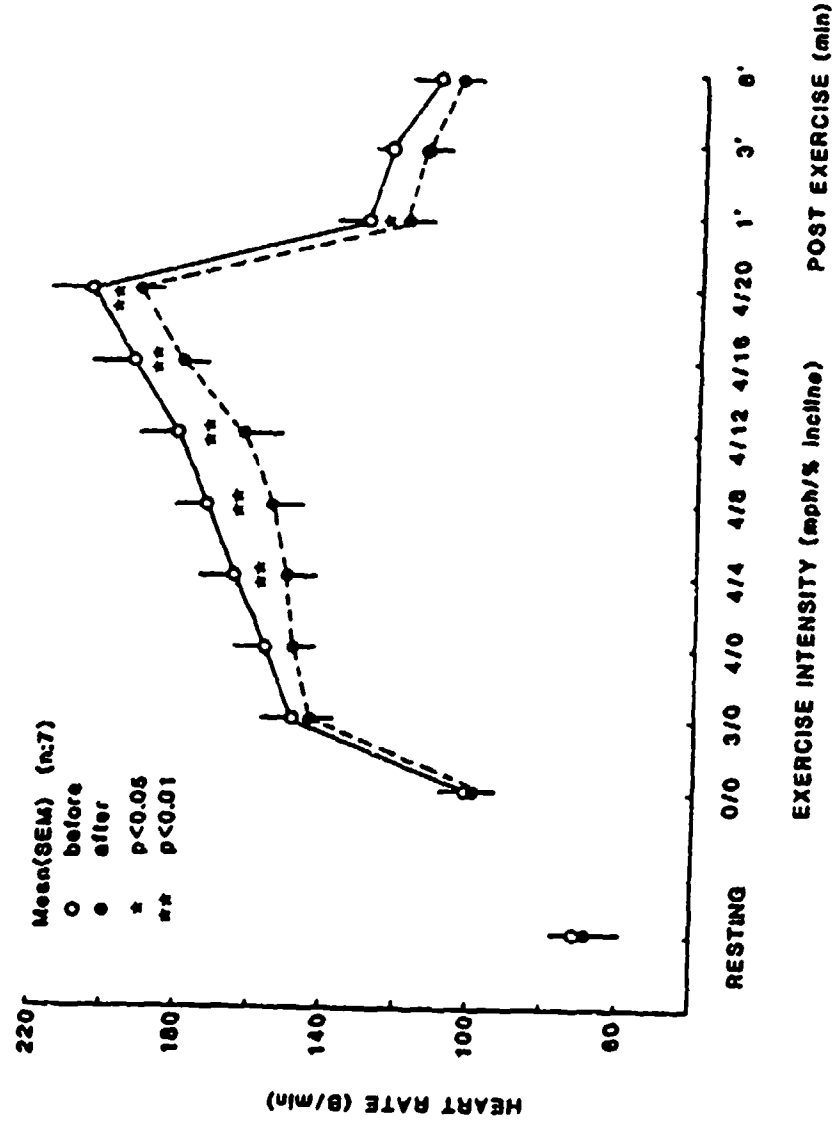
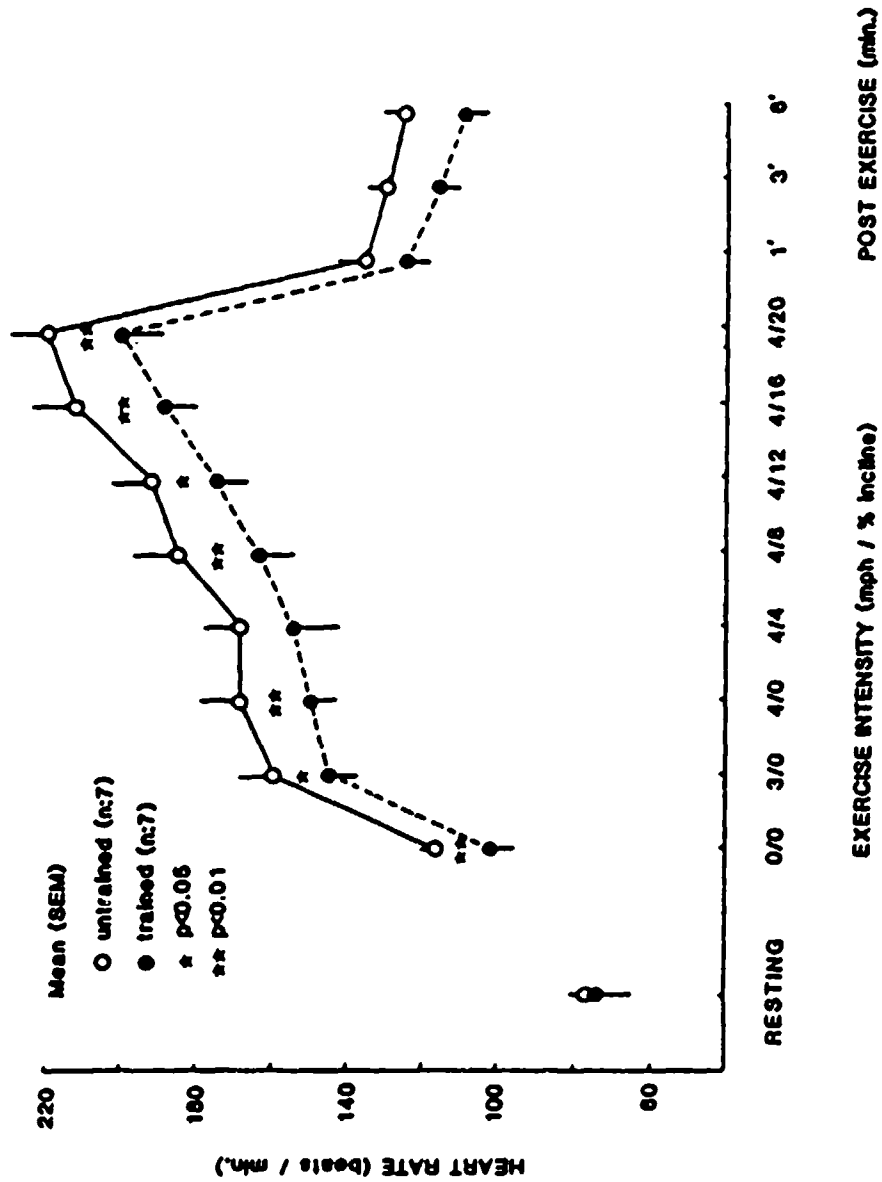


Figure 5. Comparison of heart rate responses to a submaximal exercise test of the untrained and the endurance trained dogs, at the time of the centrifuge experiment. Symbols as in Figure 3.

HR RESPONSES TO SMT AT TIME OF EXPERIMENT



difference in resting heart rate between the groups. However, the trained animals had a significantly lower rate when standing quietly on the treadmill and at every exercise intensity.

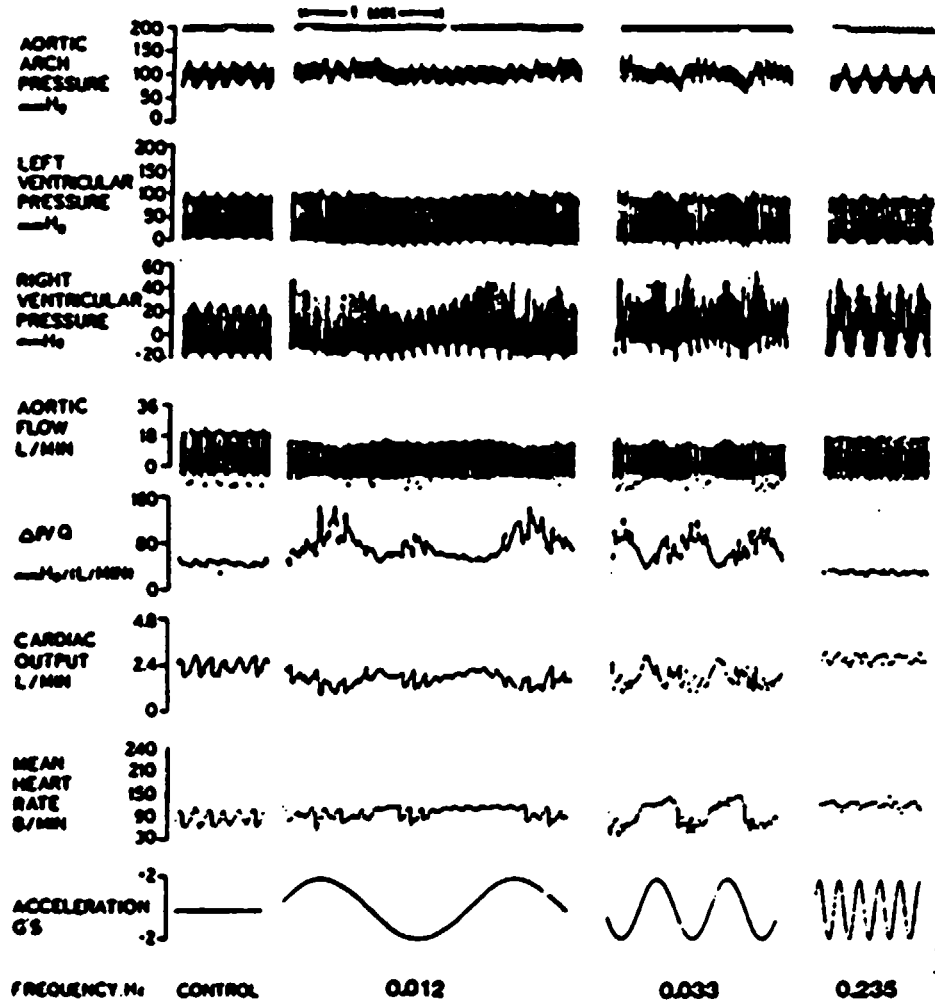
Cardiovascular Responses to Oscillatory Blood Volume Shifts.

The responses of a typical untrained dog to sinusoidal 2 Gz acceleration are shown in Figure 6. It should be recalled that a +Gz acceleration shifts blood volume from the head and thorax into the abdomen and hind limbs; a -Gz acceleration causes the opposite volume shift. Three input acceleration frequencies are shown: low (0.012 Hz), intermediate (0.033 Hz), and high (0.235 Hz).

At the lowest input frequency, aortic pressure (AP) was effectively maintained despite the sinusoidal volume shifting evident in diastolic right ventricular pressure (RVP), which reflects right heart filling pressure. Maintenance of AP is associated primarily with changes in total peripheral resistance (TPR, labelled $\Delta P/Q$), which increased as acceleration (ACC) approached its peak positive value, and fell off as ACC diminished. There were only small changes in cardiac output (CO) and heart rate (HR) during these low frequency oscillations.

At an intermediate input acceleration frequency, AP excursions were more pronounced. Oscillations in TPR were

Figure 6. Cardiovascular responses of an untrained dog to sinusoidal ± 2 Gz acceleration. $\Delta P/Q$ is an indicator of Total Peripheral Resistance. Three representative input acceleration frequencies are shown: low (0.012 Hz), medium (0.033 Hz), and high (0.235 Hz).



the same amplitude as before, but were shifted so that maximum resistance occurred at -2 Gz, i.e., when blood volume was pooling in the upper body. Heart rate increased as ACC neared its maximum, peaked shortly after $+2$ Gz, then fell precipitously to reach its minimum in advance of -2 Gz. Oscillations were also evident in CO, which peaked prior to $+2$ Gz and decreased soon thereafter.

The highest input frequency produced AP oscillations that were more symmetrical than at lower frequencies. There were no changes in TPR, and only small variations in HR and CO, during the course of this frequency exposure.

The extent to which endurance training influenced the effects of sinusoidal acceleration was assessed by comparing the responses of untrained and trained dogs across a range of input acceleration frequencies. The results of these comparisons are summarized in Tables IV and V and presented graphically in Figures 7 - 13. Statistically significant differences are indicated in the figures. The untrained animals' results are denoted by open circles, and the trained, by filled circles. The standard error of the mean is indicated by the vertical bars. The top panel of each figure presents the mean values of the variable during the control period (labelled "C"), at each frequency tested, and during recovery (labelled "R"). The middle panel presents the amplitude (labelled "half-amplitude" in Figure 2) of the first harmonic component of the

variable's response to the sinusoidal stress. The bottom panel presents the first harmonic's phase angle with respect to the input acceleration. If the first harmonic reached its maximum value before the input acceleration, it was "leading" the input; otherwise, it was "lagging." Note that a phase angle of 180 degrees can be considered as either leading or lagging.

As can be seen in Table IV, there were large effects over the range of input frequencies in every variable but diastolic LVP. These effects have been analyzed elsewhere (Marquis, 1978; Knapp et al., 1982). Because the intent of this dissertation is to document any differences between untrained and trained animals, the frequency responses themselves will be discussed only briefly. Mean diastolic LVP showed an effect due to training that was not dependent on frequency. This appears to be a nonspecific response to the acceleration stress, and as such would be of peripheral interest in this analysis. The interactions between training and frequency indicate differences between the two groups of animals that are frequency dependent, and are therefore of primary interest. Table V shows that significant differences in HR, SV, and TPR occurred in the same regions of the frequency spectrum. These differences are detailed below.

Table IV: SUMMARY ANOVA

Variable	# dogs (untr., tr.)	Effects		
		Training	Frequency	Train. x Freq.
diast. RVP	7,7			
mean		--	<0.05	--
ampl.		--	--	<0.05
phase		--	--	--
diast. LVP	7,7			
mean		<0.05	--	--
ampl.		--	--	--
phase		--	--	--
AP	7,7			
mean		--	<0.01	--
ampl.		--	--	--
phase		--	<0.001	--
TPR	7,6			
mean		--	<0.001	--
ampl.		--	<0.05	--
phase		--	<0.001	<0.001
HR	7,7			
mean		--	<0.001	<0.05
ampl.		--	<0.001	<0.05
phase		--	<0.005	--
SV	7,6			
mean		--	<0.001	<0.001
ampl.		--	<0.05	--
phase		--	<0.001	--
CO	7,6			
mean		--	<0.001	--
ampl.		--	<0.001	--
phase		--	<0.001	--

Table V: SUMMARY OF SIGNIFICANT DIFFERENCES
BETWEEN GROUPS AT EACH FREQUENCY

Variable	Frequency (Hz)									
	<u>0.008</u>	<u>0.016</u>	<u>0.025</u>	<u>0.035</u>	<u>0.045</u>	<u>0.055</u>	<u>0.072</u>	<u>0.080</u>	<u>0.150</u>	<u>0.230</u>
HR										
mean										
ampl.										
SV										
mean										
TPR										
phase										
										</

Diastolic Right Ventricular Pressure.

The sinusoidal acceleration forcing function was always of constant amplitude, and Figure 7 shows that the blood volume shifted, as reflected in diastolic RVP, was also constant. There were no differences between the untrained and trained groups at any frequency in the means, amplitudes, or phase angles. The large group differences during control and at the lowest frequency were due to high pressures in one animal, which diminished as the test progressed. There were no frequency effects across the spectrum, and no differences between control and recovery values. The amplitudes of oscillations in RVP, as reflected by the first harmonic, were unaffected by trained state and constant from 0.008 to 0.15 Hz. At 0.23 Hz, untrained diastolic RVP oscillations were larger than at 0.15 Hz ($p < 0.05$) and 0.008 ($p < 0.01$), and those of the trained group were larger than at 0.008 Hz ($p < 0.05$). These oscillations were 180 degrees out of phase across the frequency spectrum.

Diastolic Left Ventricular Pressure.

The untrained group had an average diastolic LVP that was significantly higher ($p < 0.05$) than that of the trained group, regardless of frequency (Figure 8). The first harmonic amplitudes were equal and constant up through the

Figure 7. Responses of diastolic right ventricular pressure to sinusoidal acceleration at several frequencies. Open circles represent untrained dogs, closed circles represent trained dogs, and bars represent standard error of the mean. Top panel shows mean values for both groups at each frequency tested plus control ("C") and recovery ("R") mean values. Middle panel shows the half amplitudes of the first harmonic components at each input frequency. Bottom panel shows the phase angles of the first harmonic components with respect to the input sinusoid, at each frequency.

DIASTOLIC RIGHT VENTRICULAR PRESSURE

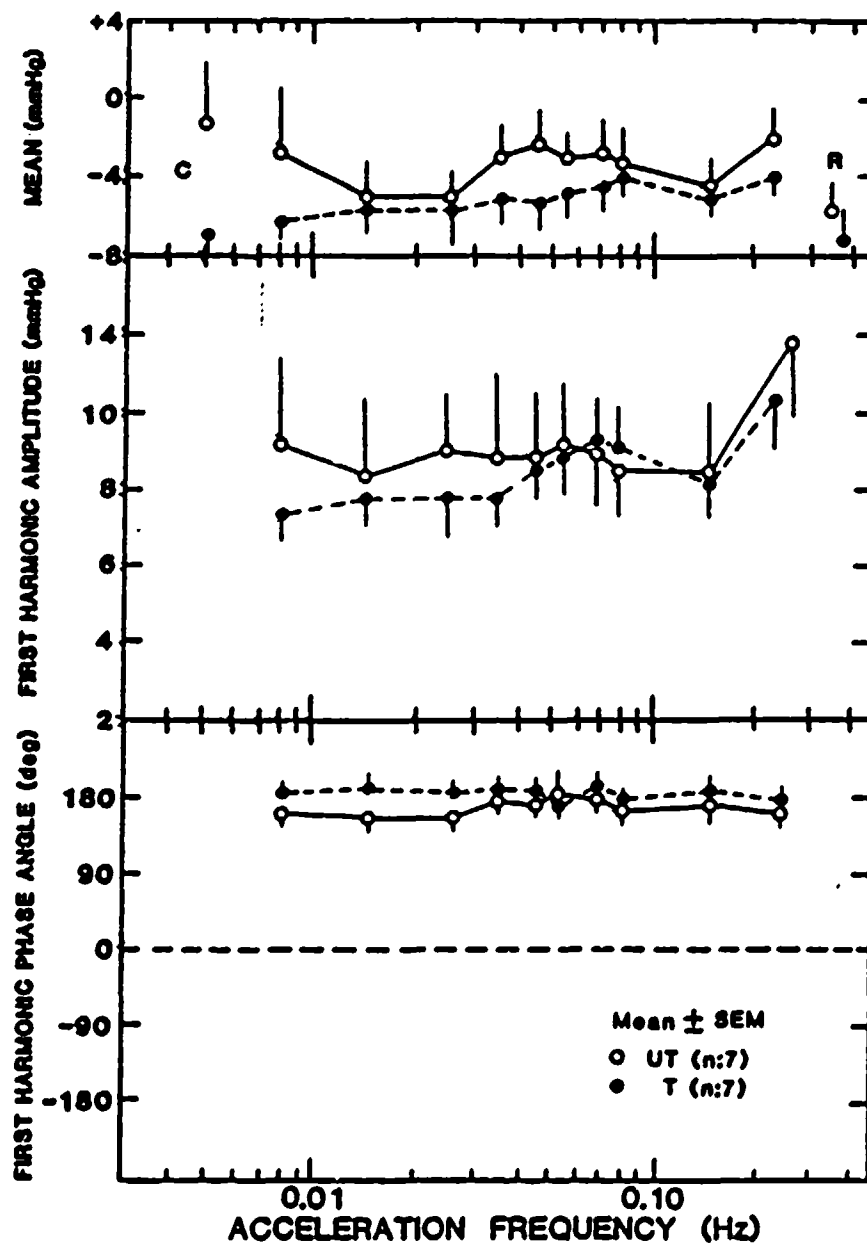
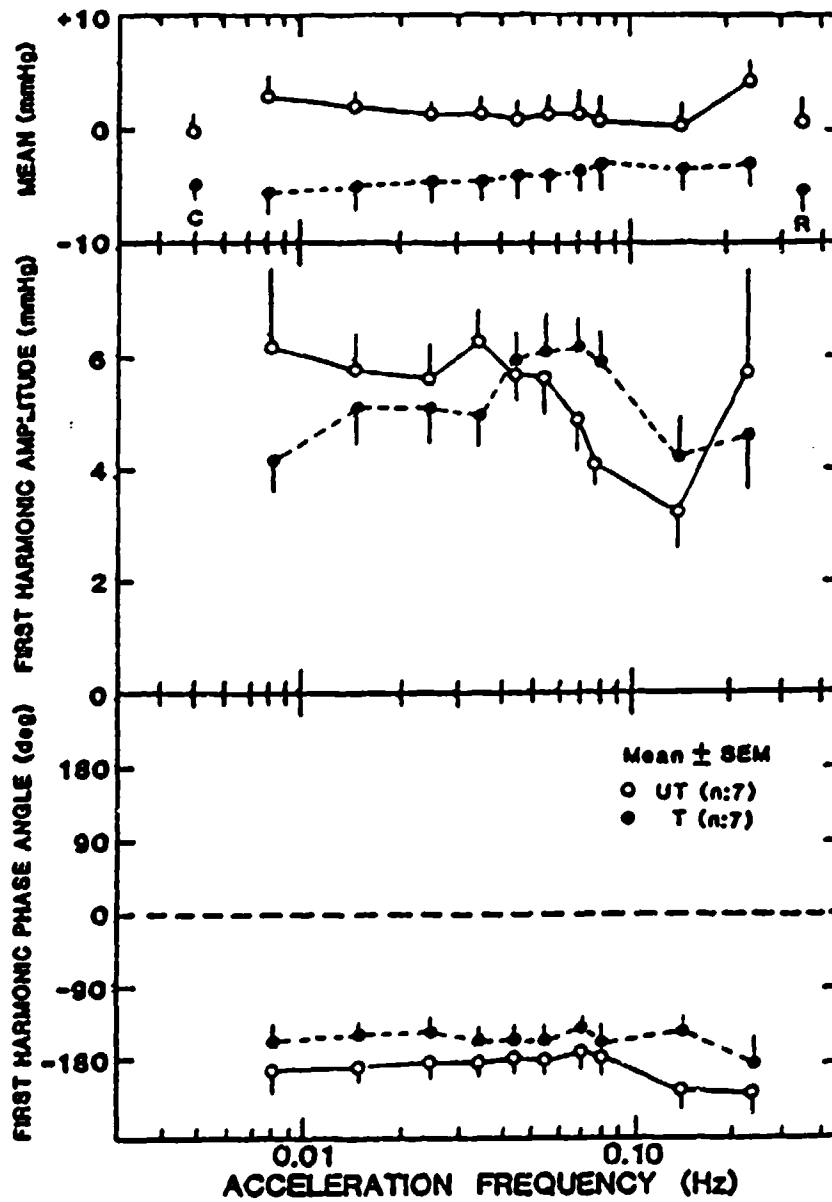


Figure 8. Responses of diastolic left ventricular pressure to sinusoidal acceleration. See Figure 7 for symbols, etc.

DIASTOLIC LEFT VENTRICULAR PRESSURE

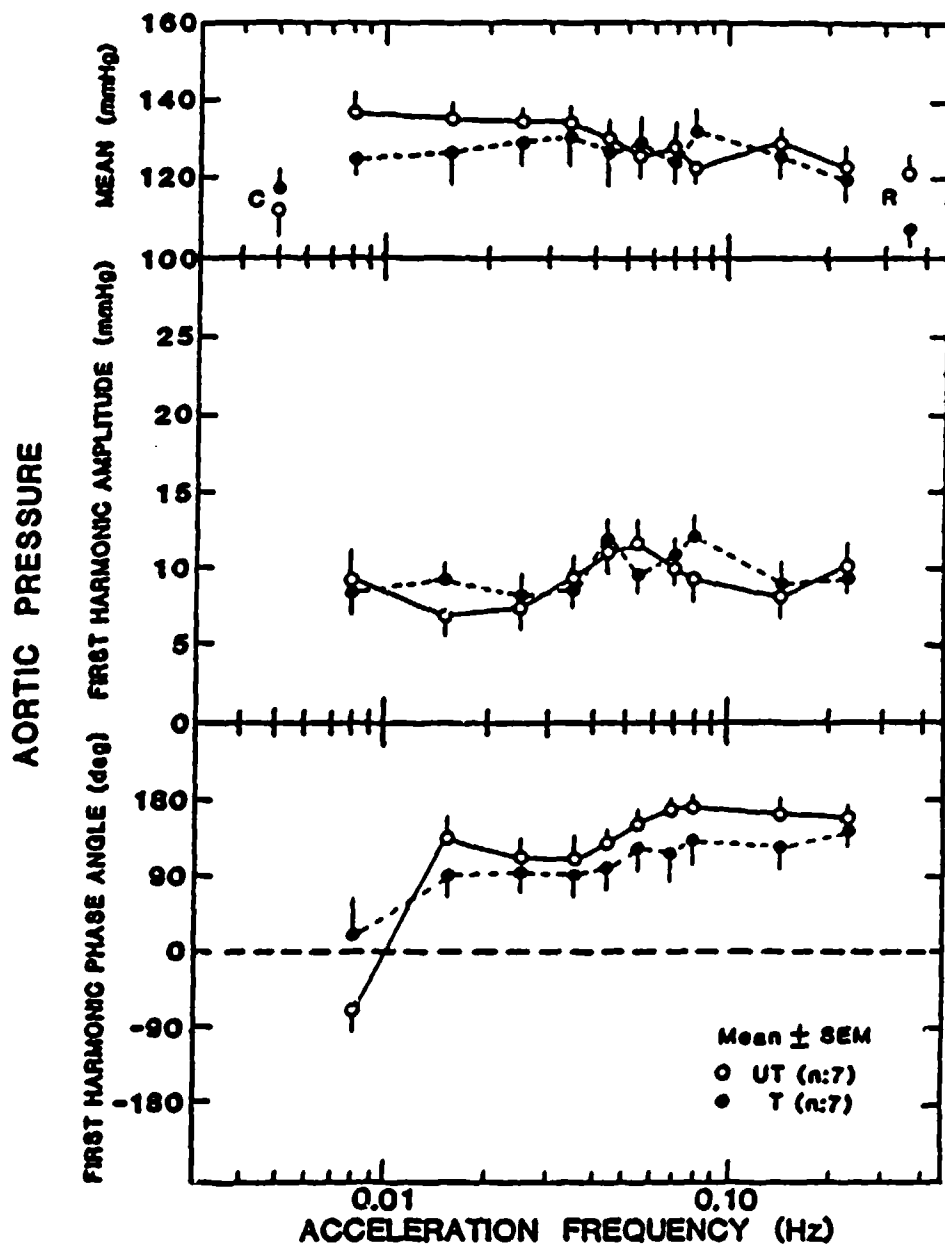


intermediate frequencies (0.035 Hz), became more variable at the higher frequencies, and then increased between 0.15 and 0.23 Hz. Both groups' diastolic LVP phase angles remained approximately 180 degrees out of phase over the frequency spectrum.

Aortic Pressure.

Aortic pressure is a fundamental indicator of cardiovascular well-being as well as the primary determinant of acceleration tolerance. Across the frequency spectrum there were no significant differences in mean AP due to trained state, although the trained animals maintained a slightly lower mean AP from 0.008 to 0.025 Hz (Figure 9). Control AP was slightly lower in the untrained animals, and increased with the stress ($p < 0.05$) more than in the trained animals. The untrained group also had a higher recovery AP than the trained group ($p < 0.05$). Overall, AP increased from control to recovery in the untrained animals, but decreased in the trained ones. First harmonic amplitudes showed no significant training or frequency effects, but there was a tendency toward larger amplitudes in the untrained dogs at 0.055 Hz as has been previously noted (Knapp et al., 1982), and in the trained dogs at both 0.045 and 0.08 Hz. In general, the phase angles of the first harmonics were significantly dependent on frequency ($p < 0.001$), largely due to the difference in phase

Figure 9. Responses of aortic pressure to sinusoidal acceleration at several frequencies. See Figure 7 for symbols, etc.

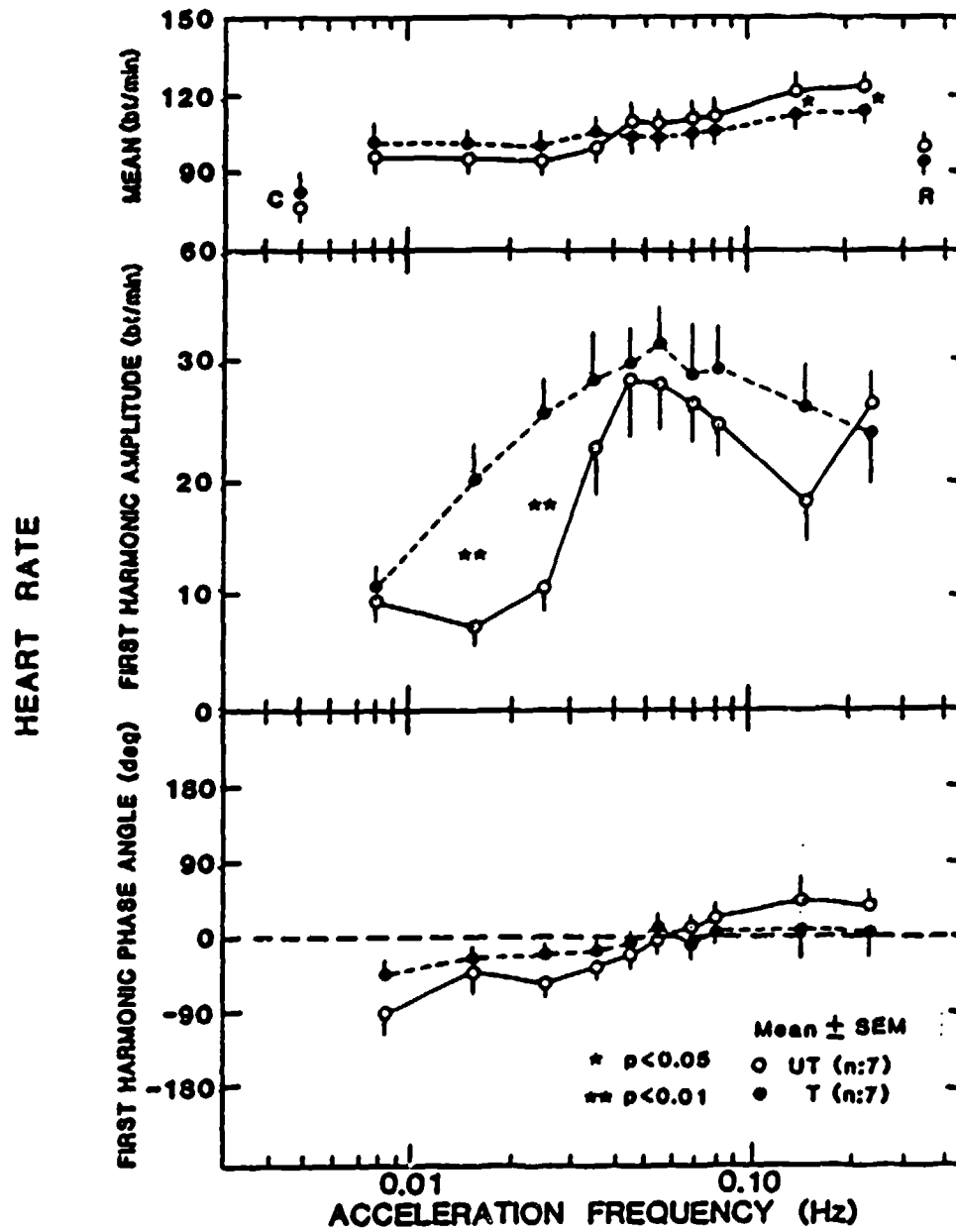


between 0.008 and 0.016 Hz in the untrained group. Oscillations in AP were in phase with or slightly leading the acceleration input at 0.008 Hz, indicating that the animals were able to increase pressure even when blood volume was being shifted caudally. At higher frequencies, the oscillations lagged by 90 to 120 degrees.

Heart Rate.

Mean HR response to the input frequencies (Figure 10) showed no training effect up through 0.08 Hz, but at higher frequencies the trained animals had a higher average HR ($p < 0.05$). From control rates of about 80 beats/minute, the mean HR increased ($p < 0.001$) with onset of the stress and remained almost constant for the duration of the test. Recovery HR was also higher than control. Heart rate responses to the input acceleration frequencies showed the distinctive frequency dependence found in previous studies (Marquis, 1978; Knapp et al., 1982). Amplitudes of oscillation were lowest at 0.008 Hz, increased to their maxima at 0.045-0.055 Hz, and gradually diminished with increasing frequency. From 0.016 to 0.035 Hz, these amplitudes in the trained animals were 25-30 beats/minute larger than in the untrained dogs ($p < 0.01$). The result is that the amplitude of HR excursions in the trained dogs increased steadily from 0.008 to 0.045 Hz, while in the untrained dogs, there was no increase until

Figure 10. Responses of heart rate to sinusoidal acceleration at several frequencies. See Figure 7 for symbols, etc.

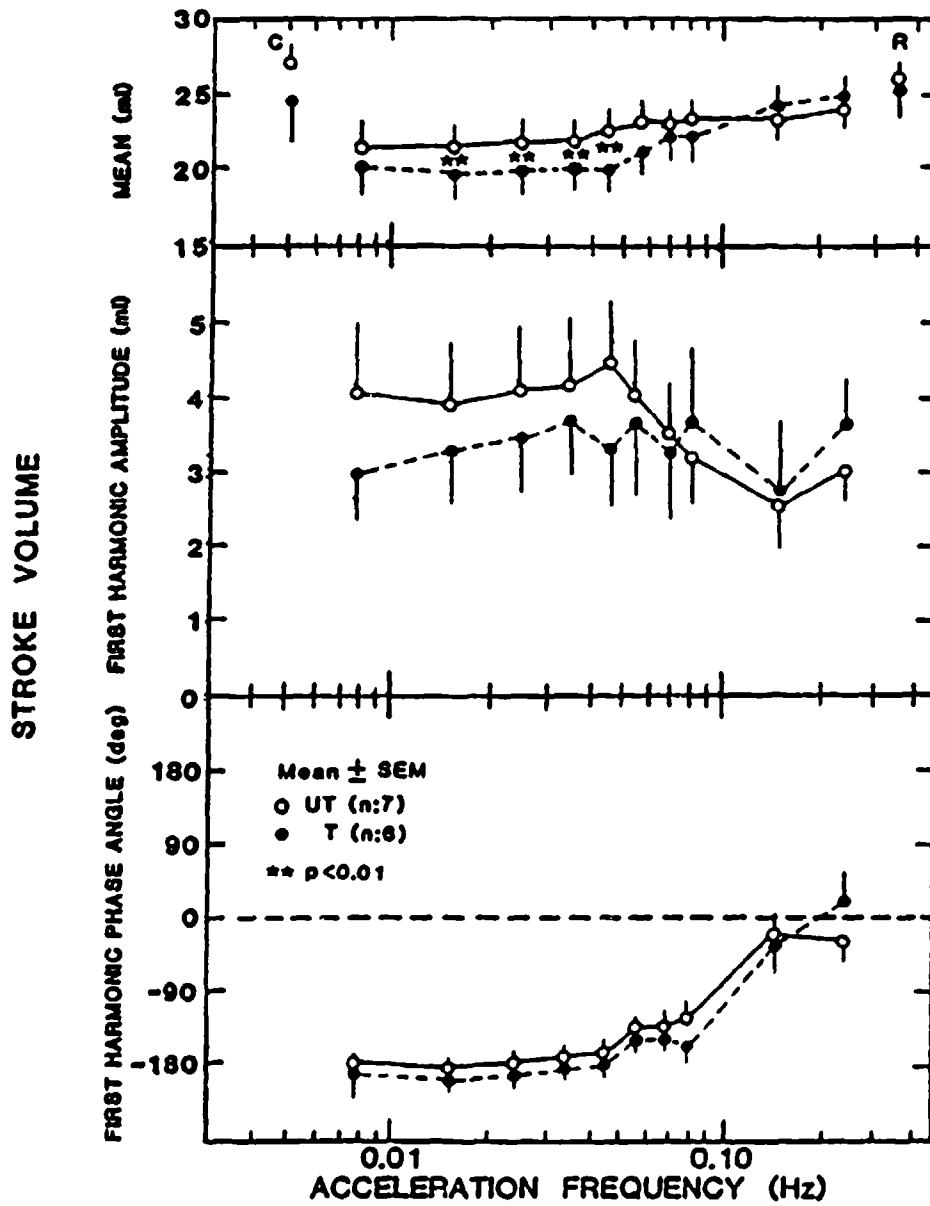


0.025 Hz, followed by a more rapid increase with frequency. The phase angles of HR oscillations were unaffected by trained state, but significantly influenced by frequency. Oscillations in HR led acceleration slightly at the lowest frequencies, were in phase between 0.045 and 0.08 Hz, and then lagged slightly at higher frequencies.

Stroke Volume.

The trained animals maintained significantly lower calculated stroke volumes than the untrained animals from 0.016 to 0.045 Hz (Figure 11), although the differences are greatly reduced when the stroke volumes are normalized by body weight. Otherwise, there were no differences in mean SV, nor between the control and recovery values. First harmonic amplitude showed no training effect, but did exhibit a significant frequency effect, remaining approximately constant from 0.008 through 0.045 Hz, declining through 0.15 Hz, then increasing at 0.23 Hz. Phase angles also did not vary with trained state, but showed a significant ($p < 0.01$) frequency dependence. Oscillations in SV were 180 degrees out of phase at the lowest frequencies, then lagged even more with increasing frequency, becoming in phase with acceleration at 0.15 Hz.

Figure 11. Responses of stroke volume to sinusoidal acceleration at several frequencies. See Figure 7 for symbols, etc.



Cardiac Output.

There were no training effects on the means, amplitudes, or phase angles of calculated CO (Figure 12). Significant increases in mean CO with increasing frequency resulted in recovery values that were larger than control values in both the untrained ($p < 0.05$) and trained ($p < 0.01$) groups. First harmonic amplitudes were independent of frequency over most of the spectrum, increasing significantly ($p < 0.05$) only at 0.23 Hz. First harmonic phase angles were uninfluenced by group effects, but showed a significant ($p < 0.001$) frequency effect, being 180 degrees out of phase with acceleration at the low frequencies, lagging further with increasing frequency, then being in phase at 0.072 Hz and beyond.

Total Peripheral Resistance.

Mean calculated TPR (Figure 13) increased slightly from comparable control values in both groups of animals, then decreased significantly with increasing frequency ($p < 0.05$). The TPR in the untrained group during the recovery period was not different from the control value, but the trained group's recovery TPR was significantly lower than its control value. The amplitude of the first harmonic was slightly higher ($p = 0.051$) in the trained than in the untrained animals over the whole frequency spec-

Figure 12. Responses of cardiac output to sinusoidal acceleration at several frequencies. See Figure 7 for symbols, etc.

CARDIAC OUTPUT

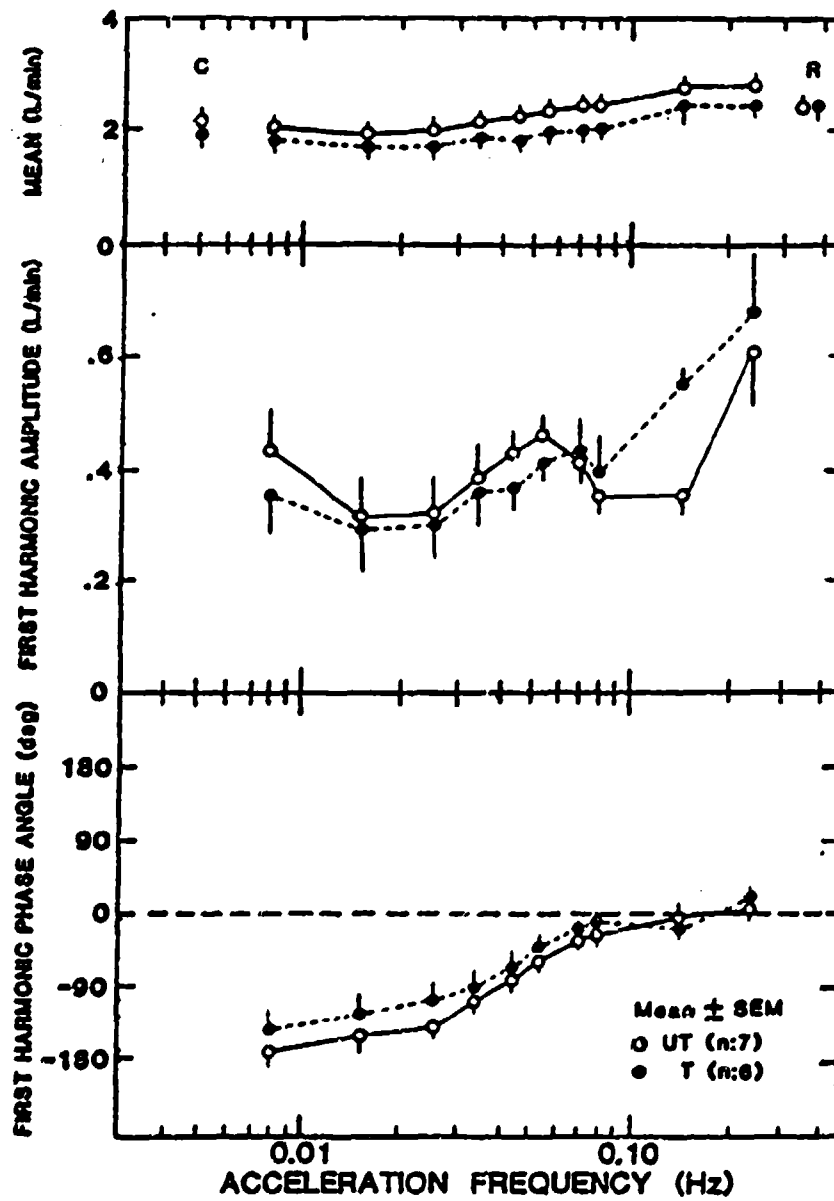
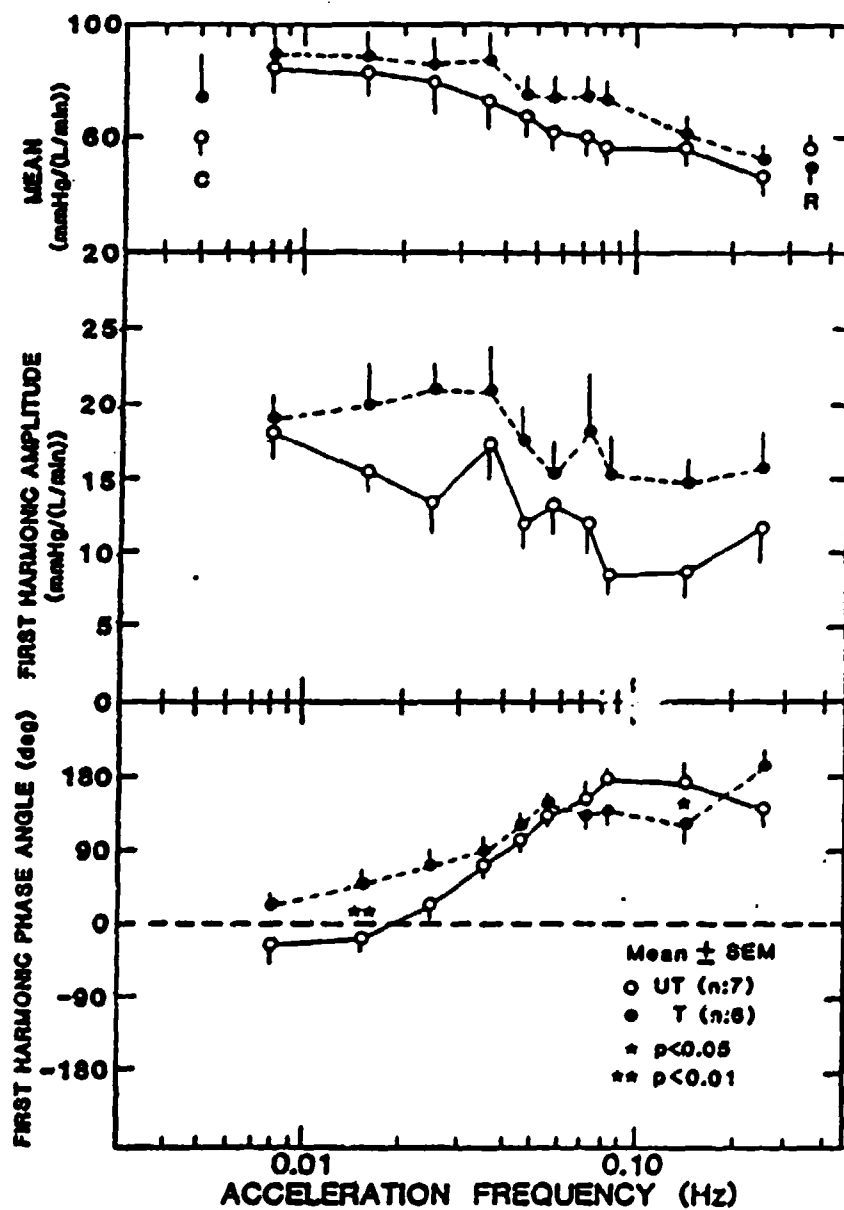


Figure 13. Responses of total peripheral resistance to sinusoidal acceleration at several frequencies. See Figure 7 for symbols, etc.

TOTAL PERIPHERAL RESISTANCE



trum. This "near-significance" was apparently influenced by the presence of amplitude values at 0.008 Hz which were almost the same in the two groups of animals, while at the other frequencies there was a clear separation between the groups (Figure 13). There was a significant effect of frequency on the first harmonic amplitudes in both groups, which were approximately constant through 0.025 Hz, and then decreased to become constant again at frequencies above 0.8 Hz. The phase angle of the first harmonic also showed a significant ($p < 0.001$) frequency dependence, being roughly in phase with acceleration at 0.008 Hz, then progressively lagging until it was out of phase at 0.08 Hz. The trained group's oscillations consistently lagged those of the untrained group through 0.035 Hz, and this difference was significant at 0.016 Hz ($p < 0.01$). From 0.072 to 0.15 Hz, the untrained group's oscillations lagged those of the trained group, significantly so at 0.15 Hz ($p < 0.05$).

Normalized Results.

Oscillations in HR showed the most pronounced tendency to reach a maximum value at intermediate frequencies. This "resonant frequency" corresponded to the small peaks in the AP and CO oscillations, to the "corner" in the SV oscillations, and to the low plateau in the TPR spectrum. Of the discrete input frequencies tested, the HR resonance

averaged 0.055 Hz in the untrained animals, and 0.071 Hz in the trained dogs (difference not significant). After normalizing the input frequencies by each animal's own HR resonant frequency, the influence of intra-group variation was reduced. Figure 14 shows the results for the HR amplitudes. The points for the binned frequencies below 16% of the resonant frequency (labelled "<0.16") were not included in the ANOVA since only 3 of the 7 untrained animals were represented. The differences in HR amplitudes between the groups are much more pronounced at frequencies below 0.75. To explore the reasons for this difference, the other variables were replotted using the same frequency bins. In Figure 15, the phase angles of TPR show a low frequency region of separation between the groups. Similarly, Figure 16 shows a region of separation in CO phase angles, where the original plot shows none. Analyses of AP and SV amplitudes and phase angles show few differences between the groups.

Finally, the possibility of altered relationships of HR and TPR to AP was explored by plotting the phase differences of HR and AP, and TPR and AP, against normalized frequency. This type of graphical analysis transforms the phase relationship information of the variables, HR and TPR, to the input acceleration sinusoid, shown in the earlier figures, into the phase angles of the first harmonics of HR and TPR with respect to the first harmonic of AP. This illustrates the physiological variables' phase

Figure 14. Amplitudes of first harmonic components of heart rate at several relative frequencies. See text for description of relative frequency, and Figure 7 for symbols.

HR AMPLITUDES vs. RELATIVE FREQUENCY

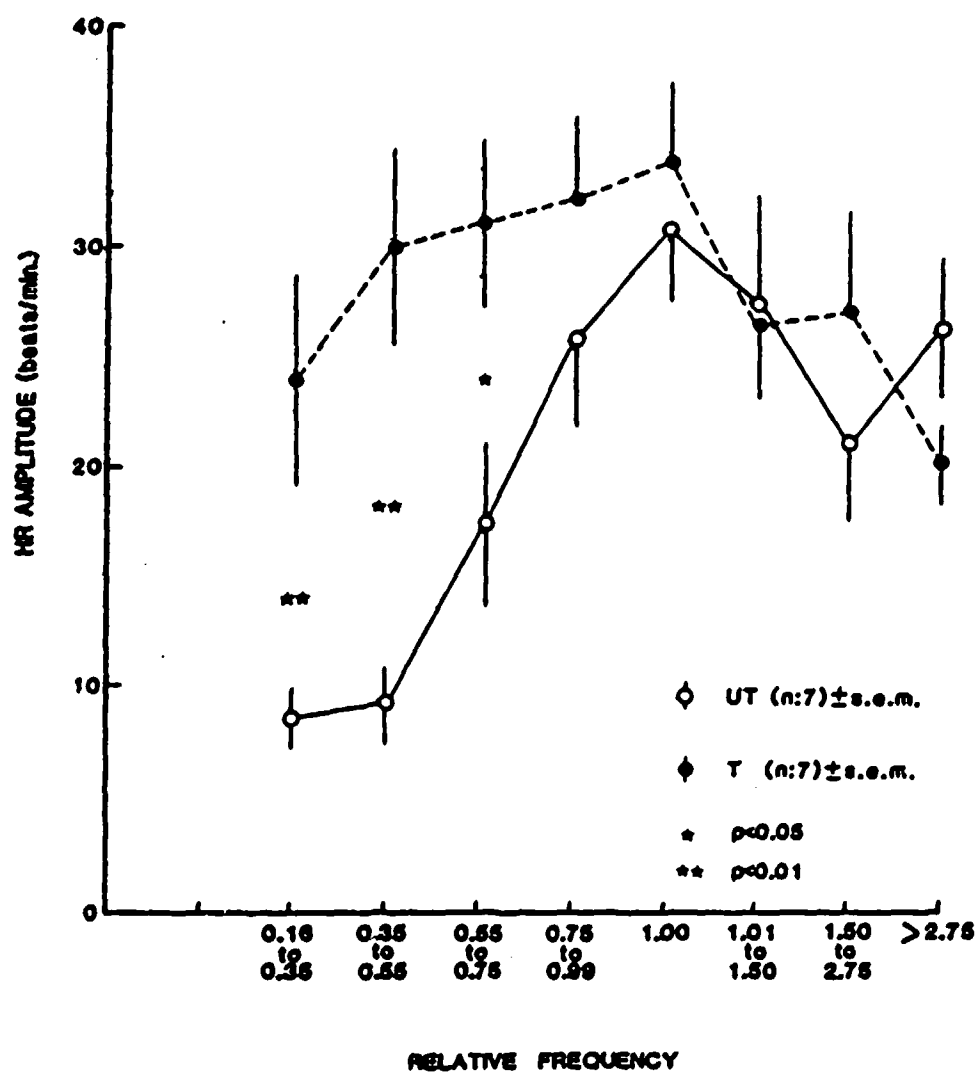


Figure 15. Phase angles of the first harmonic component of total peripheral resistance at several relative frequencies. See text for description of relative frequency, and Figure 7 for symbols.

TPR PHASE vs. RELATIVE FREQUENCY

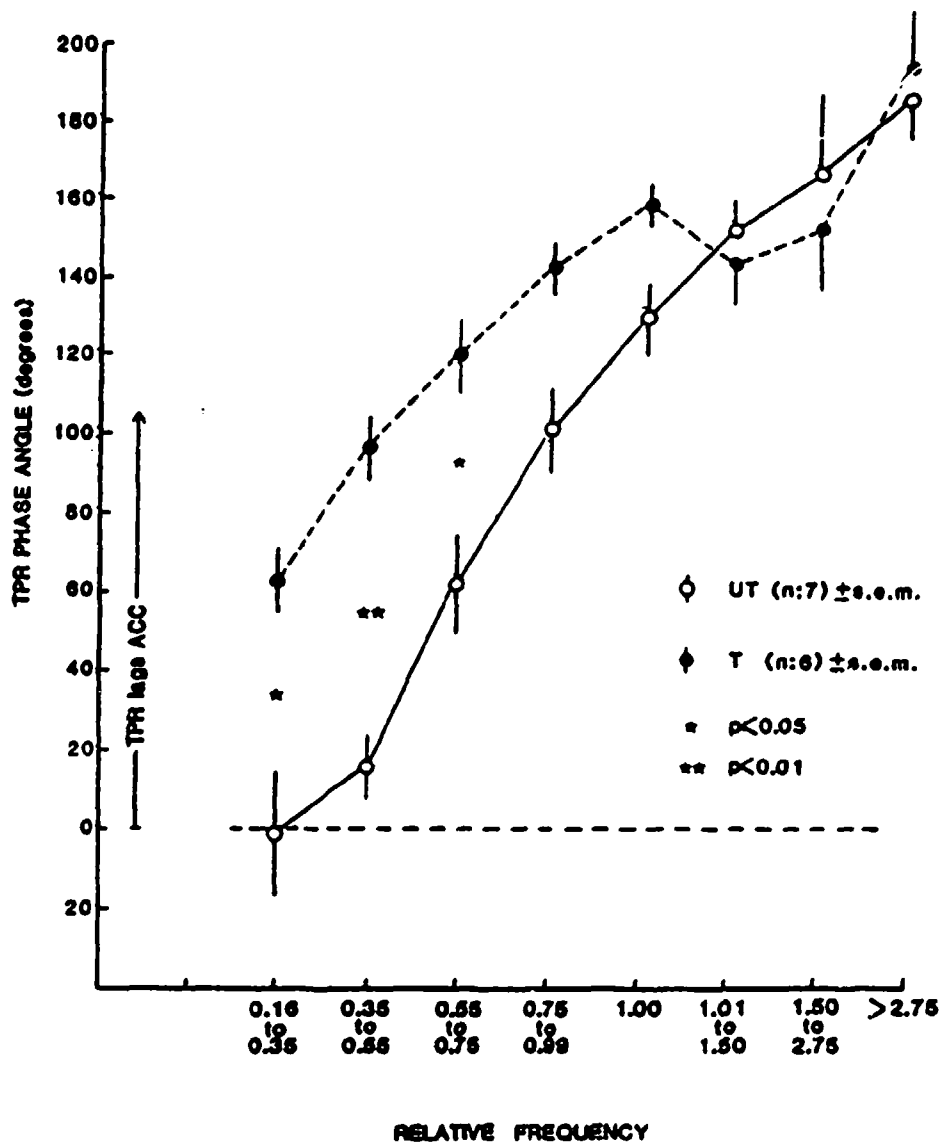
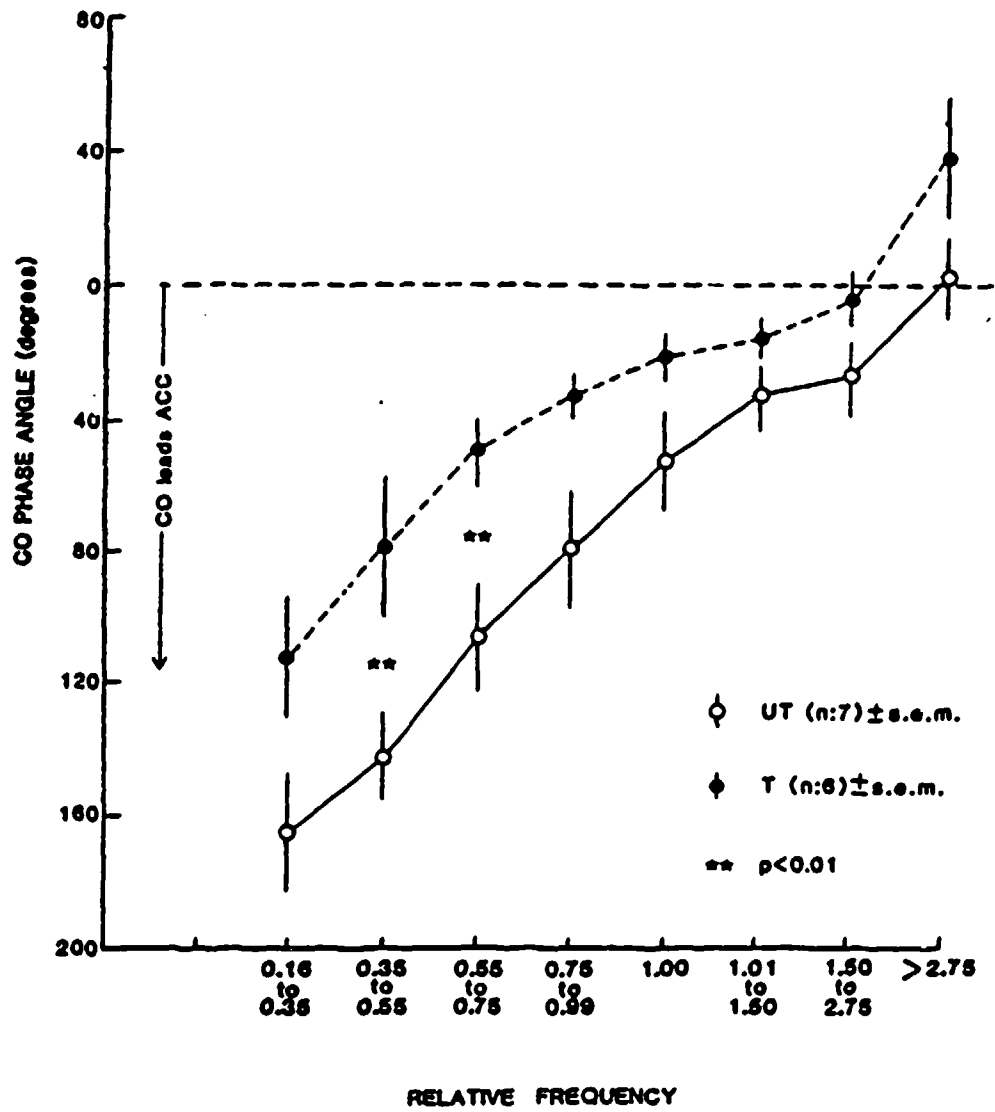


Figure 16. Phase angles of first harmonic components of cardiac output at several relative frequencies. See text for description of relative frequencies, and Figure 7 for symbols.

CO PHASE vs. RELATIVE FREQUENCY



relationships with the postulated baroreceptor stimulus, rather than with the forcing function. Figure 17 shows that at relative frequencies greater than 0.55, HR led AP in both groups. In the 0.16 to 0.35 region, untrained HR oscillations were nearly in phase with AP, while the trained HR oscillations peaked significantly earlier, leading AP by nearly 90 degrees. The trained dogs' excursions in TPR were in phase with those in AP at the lowest relative frequencies (Figure 18), while the untrained groups' TPR oscillations led AP by 90 degrees (significant, $p < 0.05$) through a relative frequency of 0.55. Thereafter, the groups did not differ significantly.

Figure 17. Algebraic differences of first harmonic phase angles of heart rate and aortic pressure at several relative frequencies. The angles indicate the angular separation between peak values of heart rate and peak values of aortic pressure. See text for description of relative frequency, and Figure 7 for symbols.

HR PHASE - AP PHASE vs. RELATIVE FREQUENCY

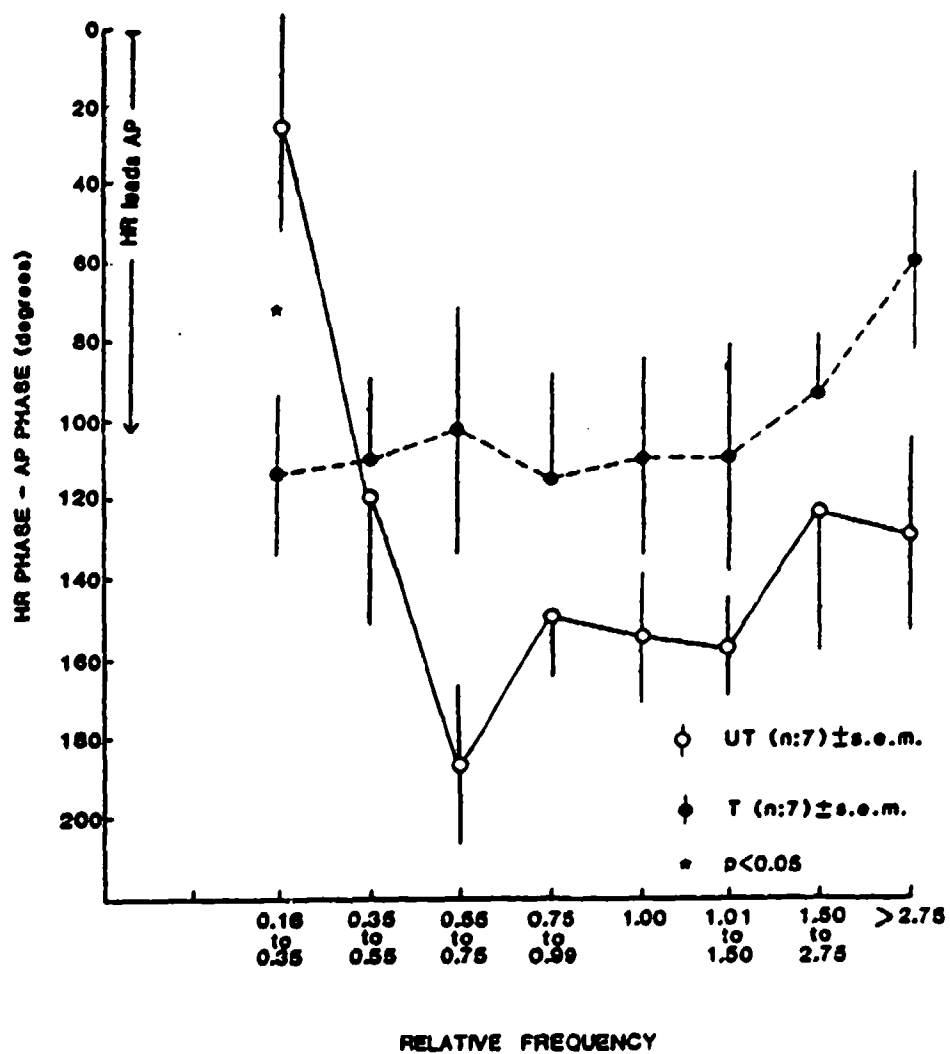
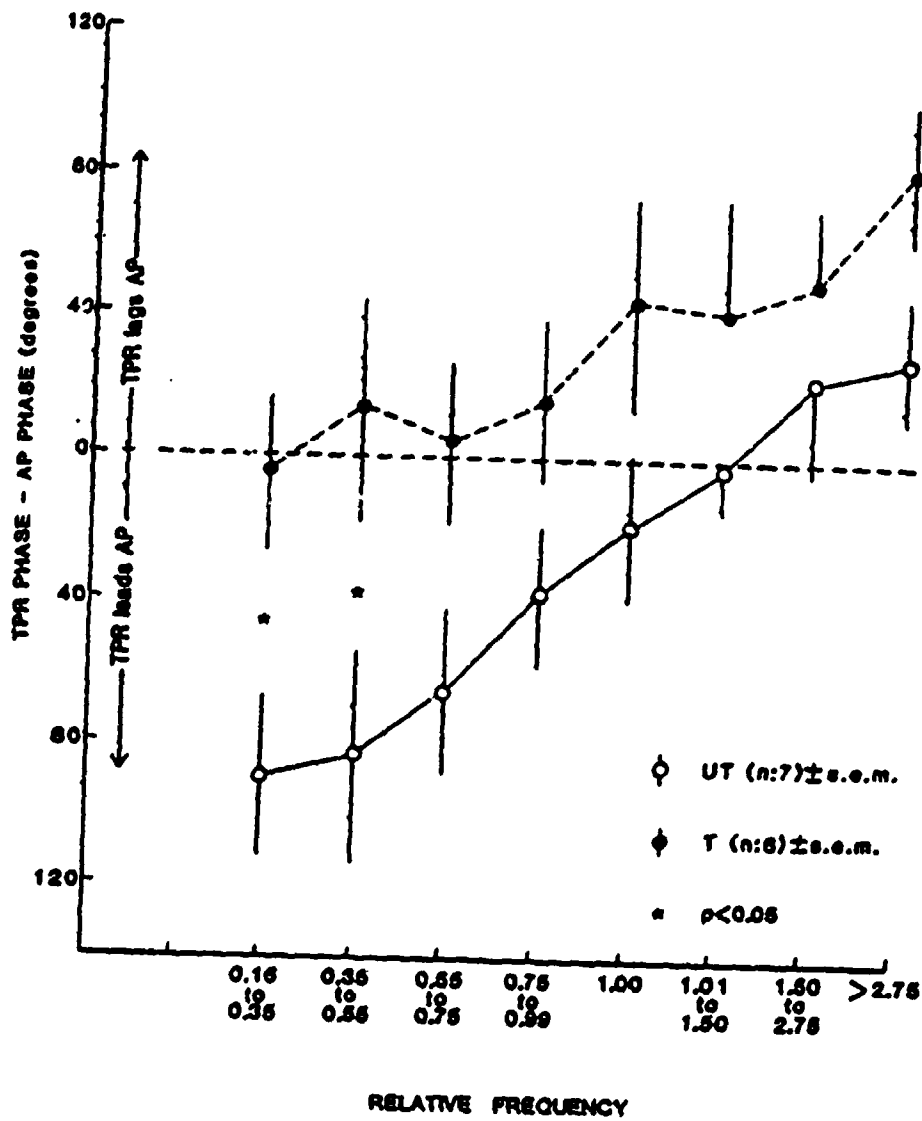


Figure 18. Algebraic differences of first harmonic phase angles of total peripheral resistance and aortic pressure at several relative frequencies. The angles indicate the angular separation between peak values of total peripheral resistance and peak values of aortic pressure. See text for description of relative frequency, and Figure 7 for symbols.

TPR PHASE - AP PHASE vs. RELATIVE FREQUENCY



DISCUSSION

This study was designed to test the hypothesis that the changes in cardiovascular regulation concomitant with endurance training influence the circulatory responses to oscillatory blood volume shifts. One group of dogs was endurance trained over a period of six weeks, and the training was verified by exercise heart rate measurements. Another group was left untrained to act as controls. Both groups of dogs were submitted to a centrifuge protocol which used sinusoidally-varying acceleration to generate the central blood volume oscillations, and their hemodynamic responses were measured.

The original experimental design called for a single group of dogs that was tested on the centrifuge both before and after training. Early experience showed that the required chronic instrumentation reduced the probability of a dog surviving a protocol of surgery, three weeks of post-operative recovery, the centrifuge protocol, six weeks of treadmill training, and then the final centrifuge experiment. Thus, a design was accepted which called for the parallel preparation of two groups of dogs, one untrained and the other trained.

The results of this study confirm previous demonstra-

tions that endurance training influences the neural regulation of cardiovascular function (Stegemann *et al.*, 1974; Claussen, 1977; Scheuer and Tipton, 1977; Paynter *et al.*, 1977; Luft, 1980; Tipton *et al.*, 1982; Blomqvist and Saltin, 1983). The unique, non-exercise stress used in this investigation provoked responses different from those previously measured. These responses and their differences from previous findings will be discussed below.

Rationale for Choice of Animal Preparation and of Sinusoidal Acceleration as the Stress.

Several considerations led to the choice of centrifugally generated oscillatory acceleration applied to chronically instrumented dogs as the protocol for this investigation. Of primary importance was the requirement that the perturbation should evoke circulatory adjustments by a normal, physiological stimulus. The stimulus of choice was blood pressure changes, as provoked by blood volume shifts within the vasculature, in the area of the baroreceptive elements. This permitted comparison of these experimental findings with previous work detailing changes in the cardiovascular control system with chronic exercise, and with the literature on the effects of acute and chronic changes in blood pressure and blood volume due to hypertension, hemorrhage, orthostatic stress, weightlessness, etc.

Blood pressure changes accomplished by the noninvasive shifting of intravascular blood volume permitted the routine use of the intact, unanesthetized (but tranquilized) animal preparation available at the Wenner-Gren Research Laboratory. This chronically instrumented, "closed chest" animal preparation eliminated the physiological disruption of the anesthesia required for acute surgery (Price and Onishi, 1980; Longnecker and Harris, 1980; Altura *et al.*, 1980).

Finally, the use of whole-body low-frequency oscillation provided a unique contribution to the literature on cardiovascular regulation and its adaptation to chronic exercise. Previous investigations (Guyton *et al.*, 1951; Taylor, 1966; Brown and Taylor, 1972; Gillingham *et al.*, 1977; Marquis, 1978; Brown *et al.*, 1981; Knapp *et al.*, 1982) had demonstrated the utility of such analyses in defining the basic characteristics of cardiovascular regulation. The application of these techniques to the endurance trained animal permitted a greater understanding of the trained circulatory system. This study could also serve as the prototype for investigations into the frequency characteristics of other clinical and experimental conditions known to alter cardiovascular regulation.

Several methods of measuring the frequency response characteristics of the intact cardiovascular system have been developed, each with advantages and disadvantages. Using random stimulation of the sino-atrial node in dogs,

Taylor (1966) generated disturbances in aortic flow which caused arterial pressure variations. Fourier analysis reduced the flow and pressure oscillations to their harmonic components. Random pacing of the SA node is a powerful and sensitive technique, but it is limited to the study of peripheral vascular responsiveness. Reflex changes in heart rate are eliminated by the pacing stimuli. In an investigation of the effects of endurance training on cardiovascular control, heart rate should be included, since it has historically been a primary determinant of the trained state (Ordway *et al.*, 1982).

Guyton (1951) developed a technique for perturbing the intact circulation by rapid hemorrhage and reinfusion of blood volume. This method has been improved (Brown and Taylor, 1972; Brown *et al.*, 1981), but involves acute surgery that requires a degree of anesthesia which may interfere with the reflexes of interest. In addition, the volume stimulus is applied first to the venous side of the circulation, and reaches the arterial side only after passing through the pulmonary circulation. This allows differential stimulation of the cardiopulmonary and arterial baroreceptors which may obscure the reflex responses of interest.

The arterial pressure stimuli for this dissertation were generated by translocating blood volume within the intact vasculature using oscillatory acceleration provided by a specially modified, large animal centrifuge. This

technique required no surgical intervention to produce the volume shifts and allowed all reflex responses to the pressure disturbances to be expressed. The global nature of the stress resulted in the simultaneous stimulation of the arterial and cardiopulmonary baroreceptors. The level of acceleration could be selected to provide any magnitude of pressure disturbance necessary. The drawbacks are few and minor. Stimulation of the vestibular system is of minimal importance, since the available evidence suggests that the vestibular contributions to circulatory control are small (Ishikawa and Miyazawa, 1980; Winter *et al.*, 1982). Secondary baroreceptors in the splanchnic circulation would encounter pressure stimuli with different amplitudes and phases than those of the arterial and cardiopulmonary receptors. However, these influences probably don't obscure the systemic effects of the major baroreceptors (Tuttle and McCleary, 1979; Kostreva *et al.*, 1980). Finally, using this technique, the Wenner-Gren Research Laboratory has accumulated a wealth of data, on dogs that were intact and in various stages of pharmacological autonomic ablation (Marquis, 1978; Knapp *et al.*, 1982). These data served as a basis for comparison with the results of this investigation.

Differences in Resting and Exercise Heart Rates Between Untrained and Endurance Trained Dogs.

There was a slight decrease in resting heart rate (HR) with endurance training (Figure 4), but no significant difference in resting HR between the trained and untrained groups (Figure 5). The same training protocol had previously produced a significant resting HR reduction (Ordway *et al.*, 1982). Failure to do so in the present study may have been due to the span of pretraining HR values (47 to 84 beats/minute) and to one animal having a higher resting HR after training than before.

However, training was associated with a significant ($p < 0.05$) within-group HR reduction of 15-20 beats/minute during treadmill running at 4 miles per hour on inclines of from 4% to 20% (Figure 4). This demonstrates that the trained group met the criterion for "trained" animals described by Stone (1977). The training regimen also established a clear difference between the untrained and trained groups in HR responses to the exercise test (Figure 5) where there was none before training (Figure 3).

Analysis of Cardiovascular Responses to Sinusoidal Acceleration Stress.

The hemodynamic responses to the oscillatory acceleration were not strictly sinusoidal. This was probably

due to the neural regulation process (Spelman and Pinter, 1978; Knapp et al., 1982). However, by signal processing techniques, a sinusoidal component of the response with the same period as the input acceleration could be determined for each input acceleration frequency (Figure 2). The amplitude of this first harmonic and its phase relationship with the input acceleration were of primary interest in this investigation. The first harmonic is only one of an infinite number of harmonic components of the total waveform. However, in none of the measured variables was there a significant difference due to trained state in second harmonic amplitude or phase angle (data not presented here). It was assumed that the same held true at the higher harmonics.

Other workers (Marquis, 1978; Knapp et al., 1982) have detailed the frequency responses of the normal canine cardiovascular system using the same acceleration stress. Therefore, this study concentrated only on the differences in those responses between untrained and trained animals.

Blood Volume Shifts as Reflected in Diastolic Right and Left Ventricular Pressures.

The effectiveness of the acceleration stress in shifting blood volume is evident in Figure 1, and in the spectra of diastolic right and left ventricular pressure (Figures 7 and 8, respectively). The absence of a consis-

tent difference between the groups in the mean, amplitude, and phase angle of diastolic right ventricular pressure (RVP) indicate that the volume stimulus was the same in both groups. The amplitude and phase angle plots (Figure 7, middle and bottom panels) show that venous return, as reflected in right heart filling pressure, is influenced by the sinusoidal acceleration, but essentially invariant with frequency up to about 0.15 Hz. At 0.23 Hz, RVP oscillations increased as the input acceleration interacted synergistically with the thoracic respiratory pumping. The constant phase angle of 180 degrees relative to acceleration confirmed the passive nature of the changes in diastolic RVP.

Diastolic left ventricular pressure (LVP) can be interpreted in essentially the same manner as diastolic RVP. The first harmonic amplitudes (Figure 8, middle panel) were only slightly more frequency dependent than in the right heart, perhaps due to the hydraulic uncoupling of the left and right ventricles by the pulmonary vasculature (Yurugi *et al.*, 1968). Since the ANOVA assumes a homogeneous variance, it is possible that the wide range of standard errors masks some significant frequency or training effects. Diastolic LVP oscillations were consistently about 180 degrees out of phase with acceleration (Figure 8, bottom panel). Mean diastolic LVP (Figure 8, top panel) showed a significant ($p < 0.05$) overall effect due to trained state, with the untrained group's mean

elevated over the trained group's. This difference is probably not an instrument artifact, since the same pressure transducer was used in every experiment, and the order of untrained and trained animal experiments was randomized. A depressed LVP has been observed in hypovolemic dogs (Quillen *et al.*, 1983). However, there is no reason to postulate a hypovolemia in the trained animals in this study, since all animals were allowed water *ad lib.* Any hypovolemia should have been apparent on the low pressure side of the circulation, but there were no between-group differences in mean diastolic RVP (Figure 7). In fact, the literature suggests that a hypervolemia, not a hypovolemia, is associated with endurance training (Scheuer and Tipton, 1977). Plasma volume was not determined in the present study.

The significant group difference in mean diastolic LVP without a similar difference in mean diastolic RVP could indicate a larger resistance, or a smaller compliance, of the pulmonary vasculature in the trained animals than in the untrained animals. Pulmonary blood flow was not measured in this study, making the determination of the resistance to this flow impossible. It is risky even to estimate this resistance by substituting aortic flow for pulmonary flow on the assumption that the flows were equal over long times (*i.e.*, at least one acceleration cycle). As shown in Figures 7 and 8, mean diastolic RVP was always lower than mean diastolic LVP in both groups of

animals, across the frequency spectrum. Calculations based on these mean pressures would give pulmonary vascular resistances less than zero. During diastole under normal conditions, LVP is less than RVP, with the pressure difference having gone to overcoming pulmonary vascular resistance. During sinusoidal acceleration, however, the diastolic ventricular pressures may have been influenced by the interaction of acceleration-induced blood volume shifts, respiratory thoracic pressure changes, and group differences in the right and left heart compliances and in the functioning of the one-way pulmonary valve remain as possible explanations for this discrepancy. The design of this study does not permit further quantification of the causes of the group differences in LVP.

Arterial Pressures During Sinusoidal Acceleration.

At the level of the ascending aorta, mean arterial pressure (AP) showed no significant effects of aerobic conditioning (Table V; Figure 9) during spinal axis sinusoidal acceleration across a spectrum of input frequencies. There was a significant ($p < 0.05$) increase in AP in the untrained group between the control period and the first acceleration frequency tested (Figure 9, top panel). During the post-acceleration recovery period, AP was slightly elevated over control levels. A similar finding has been noted in normal dogs under the same experimental

conditions by Evans *et al.* (1983), who correlated this acceleration pressor response with a significant increase in heart rate (HR). In this study, beta-adrenergic blockade with propranolol eliminated the increase in HR, but unmasked a beta-adrenergically buffered increase in total peripheral resistance (TPR). As a result, a pressor response was still evident in the beta-blocked animal. The cause of this response is unclear, but may involve an interaction between hematological, neural and hormonal mechanisms (Evans *et al.*, 1983). The trained group showed the opposite pattern (Figure 9, top panel): only a minimal pressor response to the onset of acceleration, and a large drop in pressure at the end of the stress. The fact that the pressor response is manifested over a period of many minutes suggests that it is hormonal in origin (for reasons, see Introduction). One might speculate that this discrepancy in the hormonal contribution to blood pressure maintenance is somehow related to the differences in peripheral resistance response to oscillatory acceleration, discussed below, which are associated with the trained state of the dogs. However, whatever the cause of the pressor response to sinusoidal acceleration in normal dogs, it is apparently altered in endurance trained dogs.

The amplitudes of the first harmonic of AP showed no significant training effects (Figure 9, middle panel). That is, the regulation of blood pressure excursions did not differ significantly between the untrained and endur-

ance trained animals, and the amplitudes of these excursions were approximately constant at all the frequencies tested. Overall, then, endurance training did not affect the animals' ability to minimize blood pressure disturbances. The untrained group exhibited the response pattern found previously in normal dogs (Marquis, 1978; Knapp *et al.*, 1982): larger AP oscillations at 0.045 to 0.055 Hz than at higher or lower frequencies. However, in the earlier studies, the "peak" was a statistically significant feature, while here, it was not. This lack of significance may be related to the fact that the current study analyzed only the first harmonic component of the arterial pressure response, while the other studies considered the entire response. This "peaking" is probably the result of the finite time required by the pressure regulating mechanism. By the time the pressure disturbance is detected and the appropriate efferent nervous activity generated, the disturbance has been completely reversed. Thus, the effectors are being made to respond exactly out of phase with their stimulus. Indeed, at 0.045-0.055 Hz, the AP oscillations had phase angles of about 180 degrees with respect to the acceleration input (Figure 9, bottom panel). Interestingly, the trained animals' data showed more variability across the frequency range, possibly including some "splitting" of the resonant peak expected by comparison with the untrained dogs. None of these differences was statistically significant, but they sug-

gest the existence of training effects on blood pressure control yet to be elucidated.

At the lowest frequency tested, 0.008 Hz, both groups compensated for the blood volume shifts by increasing pressure when the orthostatic stress increased. The phase angles of the AP oscillations with respect to acceleration of both groups were not significantly different, and were roughly in phase with acceleration. Therefore, at this and lower frequencies, all the animals could compensate for the blood volume shifts during oscillatory acceleration by raising or lowering aortic AP as required. Whether trained or untrained, the animals apparently relied mostly on changes in peripheral resistance to accomplish these pressure adjustments (Figure 13), since heart rate changes were minimal (Figure 10).

Differences Between the Untrained and Endurance Trained Groups in the Mechanisms of Arterial Blood Pressure Regulation.

Arterial pressure is maintained and regulated by cardiac output (heart rate and stroke volume) and peripheral vascular resistance, both of which have been shown to adapt to endurance training (Claussen, 1977; Scheuer and Tipton, 1977; Blomqvist and Saltin, 1983). Table V shows that there were significant differences between the untrained and endurance trained groups in both the cardiac

and the peripheral vascular mechanisms, primarily in the frequency range from 0.016 to 0.045 Hz. Other studies (Marquis, 1978; Knapp *et al.*, 1982) have demonstrated that cardiovascular responses in this portion of the frequency spectrum are due to neurally regulated changes in peripheral resistance and heart rate (Tables II and III). Group differences in this range clearly indicate that endurance training affects neural regulation of the circulation.

Experiments on dogs suggest that it is the carotid sinus baroreceptors which contribute most to the reflex adjustments to changes in blood pressure or pulse pressure (Angell-James and Daly, 1970; Dampney *et al.*, 1971; Edis, 1971). Knapp *et al.* (1982) have found that the amplitudes of carotid sinus pressure oscillations, in response to sinusoidal acceleration, were similar to, but 1.5 times greater than, those in the aortic arch. Therefore, the phase relationship of aortic pressure to acceleration should reflect that of carotid sinus pressure.

Differences in the Cardiac Components of Arterial Pressure Regulation.

Heart rate (HR) oscillations at acceleration frequencies of 0.016 and 0.025 Hz were found to be larger in the trained compared to the untrained animals (Table V; Figure 10). These oscillations were centered on mean HR values which were slightly higher in the trained group. When the

means and the oscillations are considered together, they result in HR first harmonic maxima which were higher in the trained than in the untrained animals. There were almost no differences in the corresponding minima. This tendency toward a larger inter-group difference in the HR maxima than minima was not an artifact of the data processing procedures, because it was present in data (not presented) based on the absolute HR maxima and minima, determined by hand from the original polygraph records of the experiments. Knapp *et al.* (1982) concluded that the HR response of the normal (untrained) dog to the oscillation-induced pressure disturbances suggests a high "background" sympathetic tone modulated by parasympathetic activity during that portion of the acceleration cycle when AP increased as blood was shifted headward. Thus, the HR maximum during each oscillation seems to be a function of the background sympathetic tone, while the minimum HR represents the vagal modulation of that tone. The larger HR variations in the trained animals reflect a higher HR maximum during each cycle than in the untrained animals. The minimum value during each cycle is comparable in both groups. These HR data imply an enhanced responsiveness to sympathetic stimulation in trained dogs, or a background sympathetic tone that was relatively higher in the trained animals. Correspondingly more vagal activity was required to modulate the HR during the periods of increasing blood pressure.

When each animal's HR data were normalized by the frequency at which the animal's HR first harmonic amplitude was maximum ("resonant HR frequency"), HR oscillations in the trained group were significantly larger than in the untrained group at 16% to 75% of the resonant frequency (relative frequencies of 0.16 to 0.75 in Figure 14). Aside from making the difference even more dramatic, this method of analysis minimizes intra-group variability, and facilitates the discrimination of training effects in other cardiovascular variables which could influence the HR responses. Examples of this are provided below.

Mean stroke volume (SV) was significantly lower in the trained group than in the untrained group over the range of frequencies from 0.016 to 0.045 Hz (Table V; Figure 11). This is interesting in light of the group differences in mean diastolic LVP. The lower mean diastolic LVP in the trained group suggests a relatively reduced filling of the left ventricle, which would lead to a smaller SV. The slightly higher mean HR in the trained group produced mean cardiac output (CO) in the trained dogs that was comparable to that in the untrained animals.

The significantly smaller mean stroke volumes and slightly lower SV oscillations in the trained group than in the untrained group yielded SV maxima that were lower in the trained group, while the minimum values were relatively similar. Knapp *et al.* (1982) found that, in untrained dogs during sinusoidal acceleration, SV was least

during +2Gz (blood shifted caudally) and greatest during minus 2Gz (blood shifted cephalad). Thus, the trained dogs had their smallest SV when central blood volume should have been largest. If the total blood volumes of the two groups were comparable, as seems indicated in the diastolic RVP data, then the group difference may have been the result of impaired left ventricular filling. This possibility is supported by the diastolic LVP results, which should reflect left ventricular filling pressure. The significant differences between the groups in mean diastolic LVP and the slightly smaller amplitudes of the first harmonic of diastolic LVP indicate that, during minus 2Gz, when LVP is at its maximum (Figure 6), the left ventricular filling pressure in the trained group is still substantially smaller than that of the untrained group, assuming both groups to have the same left ventricular compliance. Whether this group difference is due to a smaller circulating volume, a larger pulmonary vascular resistance, or some other factor, is beyond the scope of this study.

Differences in the Peripheral Vascular Component of Arterial Pressure Regulation.

Total peripheral resistance (TPR), as computed in this study, showed a significant ($p < 0.05$) first harmonic phase angle difference between the untrained and trained groups

at 0.016 Hz. (Table V; Figure 13). Mean TPR values did not show any training effects, but the first harmonic amplitudes were larger in the trained group ($p=0.051$). The phase angle data suggest that the TPR response to the acceleration stress was significantly delayed in the trained animals compared to their untrained controls. The amplitude data imply that the delay in the resistance response, in the face of an increasing blood volume shift and concomitant baroreceptor stimulation, caused an increasing "error" between the resistance required to maintain AP and the level actually achieved. When the TPR finally reached its maximum, it attained higher levels than in the untrained group. This suggests that the ongoing, unrelieved "error" signal prompted a larger sympathetic outflow to the periphery than occurred in the untrained animals. This may have caused an "overshoot" in which peripheral resistance oscillations in the trained animals reach higher amplitudes than in the untrained animals, over most of the frequency range. The TPR differences are more pronounced when plotted against relative input frequency (Figure 15). Using this format, the large group differences in amplitudes of HR excursions can be related to other cardiovascular differences unobscured by intra-group variability. At relative frequencies of 16% to 75% of resonant HR frequency, TPR phase angles were significantly larger in the trained group than in the untrained group (Figure 15). This illustrates even more

clearly the lag in TPR response to acceleration in the trained animals. This is the first demonstration of a training effect on the the time course of the TPR response to a circulatory stress. Previous efforts (Luft, 1980; see also: Claussen, 1977; Blomqvist and Saltin, 1983) have been concerned only with the intensity of the TPR response.

Frequency Dependent Differences in Cardiovascular Responses to Sinusoidal Acceleration Between Untrained and Trained Dogs.

The results of this study demonstrate that both untrained and endurance trained dogs were able to maintain and regulate their arterial blood pressure in the face of oscillatory acceleration. The means by which they accomplished this, however, differed with the trained state. In the region of approximately 0.016 to 0.055 Hz, where neural control of HR and TPR are the predominant mechanisms of blood pressure control (Marquis, 1978; Knapp *et al.*, 1982), the untrained animals compensated for blood volume shifts by adjustments in TPR, while endurance-trained animals relied more on HR. Because of the lag in TPR in the trained animals, there is an increasing "error" between the actual level of resistance and that required to maintain AP. Other legs of the cardiovascular system, primarily the heart, compensate. As a result, AP is

maintained, but at the expense of some of the cardiovascular "reserve capacity." That is, the trained animals countered the ongoing stress by using energy that the untrained dogs did not need to expend, and thus had in reserve for future stresses.

The group differences in HR and TPR oscillations don't extend below about 0.01 Hz. This can be understood in terms of the portions of the frequency spectrum in which the various vascular beds are most active. From Table III, it is apparent that the contribution of the splanchnic circulation to TPR is greatest below about 0.01 Hz, while the skeletal muscle vasculature is active up to about 0.04 Hz. In this study, endurance training was associated with a significant difference in TPR phase at a frequency of 0.016 Hz, but not at 0.008 Hz. These effects can be predicted if it is assumed that the regulation of blood flow in the skeletal muscles is affected by endurance training, but that of the viscera is not. This assumption is supported by the finding (Claussen, 1977) that, unlike the skeletal muscle, the splanchnic blood flow response to maximal exercise is not affected by training. While the stress of maximal exercise is not the same as that of acceleration, this finding supports the assumption of unequal effects of endurance training on the regulation of blood flow in different vascular beds during stress.

Possible Causes of HR and TPR Differences.

The transduction of acceleration-induced volume displacements into the appropriate signals to the central nervous system by the arterial baroreceptors is necessary for the control of HR and TPR. The oscillations in mean arterial pressure showed no significant training effects in its responses to sinusoidal acceleration at frequencies from 0.016 to 0.055 Hz, indicating that there were no differences between the groups in the adequacy of the mean arterial baroreceptor stimulation. Therefore, any differences in the response of HR and TPR to the volume shifts must be a result of alterations in the carotid sinus baroreceptor reflex control of the effectors, or in the responsiveness of the effectors themselves, rather than in the adequacy of the pressure stimulus to the baroreceptors. The precise location of the difference within the baroreceptor-effector loop cannot be determined from either these data or the available literature.

Thus far, each variable has been presented in terms of its time relationship to the oscillatory input acceleration. That is, the angular separation of the maximum (or minimum) of the variable's first harmonic component and of the maximum positive (or negative) acceleration has been reported as the "phase angle" of that variable with respect to the input acceleration. However, it is not the acceleration, *per se*, but rather the results of that

acceleration, which provoke the measured physiological response. The acceleration forces the intravascular mass of blood to some location within the vessels. There, the blood's presence distends the walls of the vessel to a greater or lesser extent than existed previously. If the distended section of blood vessel includes the baroreceptor elements, then these elements are deformed, and the appropriate neural reflex is initiated. In an attempt to examine the relationship of the baroreceptor stimulus with the effector response, the phase angle of the stimulus (arterial pressure) was subtracted from the phase angle of the effector response (heart rate or peripheral resistance). Although this analysis provides only the relationship between the first harmonic component of the response with that of the stimulus, it helps to illustrate the actual stimulus-response relationship.

The phase relationships of HR and TPR to AP are plotted in Figures 17 and 18, which depict the algebraic differences of the first harmonic phase angles of HR and AP, and TPR and AP, respectively, across the range of relative frequencies. In this way, the relationship of the effectors' responses to the pressor stimulus at the baroreceptors can be examined directly. Admittedly, these figures compare only the first harmonic phase angles' responses to sinusoidal acceleration, and the frequency scale is "post-hoc" and relative. Nevertheless, the regularity of the distributions within each of the frequency

bins supports the validity of using this technique to provide a clear picture of averaged response to the input acceleration frequencies.

Figure 17 illustrates the relationship between oscillations in heart rate and blood pressure in the untrained and trained animals. At less than 35% of the resonant HR frequency (that is, at relative frequencies below 0.35), the untrained dogs had HR oscillations that were practically in phase with AP, as indicated by the phase angle of almost zero. In the trained dogs, HR variations led those in AP by about 100 degrees, and the difference between the groups was significant ($p < 0.05$) at relative frequencies of 0.16-0.35. In the untrained dogs, HR was increasing almost simultaneously with AP, and probably contributed to the pressor response. In the trained animals, HR peaked well in advance of pressure, suggesting that the role of the HR increase in the pressor response was somewhat different in the two groups. Since HR amplitudes were larger in the trained group, conceivably the absolute HR levels were comparable in both groups at the time of maximum pressure. The immediate HR history would not necessarily have been the same. For example, HR would have been near its maximum at that point in the untrained dogs, but in the trained dogs it could have been dwindling from an even higher maximum at the corresponding time in the trained dogs.

At higher relative frequencies, the untrained group's

HR oscillations moved ahead of AP by about 160 degrees, and were not significantly different from those in the trained group. Both groups of animals had roughly the same phase relationship of HR to AP, indicating HR plays a comparable role in the maintenance of blood pressure in untrained and endurance trained dogs at these frequencies.

The oscillations in TPR in the untrained animals led those in AP by 80-100 degrees at relative frequencies of 0.16 to 0.55, while those in the trained animals were in phase with AP over the same range (Figure 18). These phase differences were significant ($p < 0.05$), but gradually decreased with increasing frequency. This lag indicates that TPR takes longer to respond effectively to an arterial baroreceptor stimulus in the trained group than in the untrained group.

Other investigators have reported training-induced changes in the carotid sinus baroreceptor reflex control of the periphery (Stegemann *et al.*, 1974; Tipton *et al.*, 1982). The application of a negative pressure to the neck, increasing the carotid sinus transmural pressure and stretching the baroreceptors, induced a reflex increase in AP which was smaller in trained humans compared to untrained controls (Stegemann *et al.*, 1974). Similarly, lower body negative pressure (LBNP) caused blood pressure changes in untrained rats that were profoundly altered by sino-aortic denervation, while the blood pressure changes in trained rats were unaffected by denervation (Tipton *et*

al., 1982). These studies point to a training-induced reduction in the sensitivity of carotid sinus reflex control of the periphery. Such an explanation is consistent with the findings of this investigation.

A training effect on the baroreceptor control of peripheral resistance could conceivably occur at one or more points in the baroreceptor-effector reflex arc: a change in the baroreceptor transduction of pressure disturbances; altered afferent or efferent nervous transmission; or a difference in central processing of the baroreceptor signal (Korner, 1979; Abboud, 1982). Unfortunately, the literature has only just established that such a training effect occurs (Stegemann *et al.*, 1974; Clifford *et al.*, 1981; Tipton *et al.*, 1982). Its location within the reflex arc cannot yet be specified. However, by comparison with other conditions associated with changes in cardiovascular regulation, some assessment of possible sites can be made.

Baroreceptor reflex alterations are associated with both arterial hypertension (McCubbin, 1958) and hypotension (Salgado and Krieger, 1976). Structural changes with hypertension in both the arterial baroreceptors themselves (Angell-James, 1973) and in the vascular walls in which they are found (Sapru and Krieger, 1979; Sapru, 1980) have been documented. This could interfere with stimulus transduction. Centrally, altered processing of the baroreceptor signal has been demonstrated in the bulbar, suprabul-

bar, and spinal neurons involved in the baroreflex (Gonzalez *et al.*, 1983). Structural changes at the arteriolar level have been observed with hypertension (Folkow, 1978), but other effector alterations apparently have not been demonstrated. Similarly, little is known about changes in the functional characteristics of the afferent or efferent neural pathways which may be responsible for differences in cardiovascular regulation. However, Andresen *et al.* (1978) have shown that hypertension does not change the number of aortic nerve fibers. So far, no portion of the baroreceptor reflex arc has been ruled out as the site of a hypertensive, hypotensive, and presumably an endurance training effect.

The trained animals' sluggish TPR responses to blood pressure changes were compensated for, since the AP responses to the sinusoidal acceleration did not differ significantly between the groups of animals. At certain input acceleration frequencies, TPR phase difference between the groups was associated with significantly larger HR oscillations in the trained than in the untrained animals. This HR activity may be largely responsible for the two groups' similarity in mean pressures maintained during the acceleration stress. However, the stimulus for this increased HR variability is not clear. Studies in endurance trained humans (Stegemann *et al.*, 1974; Clifford *et al.*, 1981) revealed a smaller HR response to steady-state carotid sinus pressure changes than in sedentary

controls. A larger oscillatory HR response in the trained animals, in the absence of a corresponding difference in mean AP variations, requires either that the "gain" of the HR response to baroreceptor stimulation has been increased, or that HR be responding to some baroreceptor, or other cardiovascular, stimulus besides the changes in mean AP. The studies of Stegemann *et al.* (1974) and Clifford *et al.* (1981) suggest that, at least in humans, the gain of the HR baroreflex is decreased with training, not increased. Therefore, the likely answer is the different cardiovascular stimulus.

Arterial baroreceptor activity has been shown to be a function of both the distending pressure in the artery (Heymans and Neil, 1958) and the rate of pressure change (Scher, 1967). The distending pressure is the mean arterial pressure. Its rate of rise is reflected in the arterial pulse pressure. Lower body negative pressure (LBNP) experiments in man have shown that HR can be increased significantly in association with changes in arterial pulse pressure, even when there are no changes in mean blood pressure (Johnson *et al.*, 1974). If, as discussed above, the group differences in HR oscillations can't be related to the variations in mean AP levels, there remains the possibility that pulse pressure is at least partly responsible.

Arterial pulse pressure was not analysed directly in this study, but some inferences about its characteristics

can be made nonetheless. The pulse pressure, as the difference between maximum systolic arterial pressure and minimum diastolic pressure, is increased by the factors which increase systolic pressure and decrease diastolic pressure (Rushmer, 1976). The systolic pressure is determined largely by the left ventricular stroke volume, the peak rate of ejection, and the arterial capacitance. The diastolic pressure is primarily a function of the factors which regulate the outflow of aortic blood volume: the vascular resistance to the outflow (TPR) and the time between successive increments in aortic blood volume (cardiac interval, the inverse of HR).

The arterial baroreceptors' afferent activity is proportional to the rate of rise of pulse pressure (Scher, 1967), as well as to mean blood pressure (Heymans and Neil, 1958). The rate of pressure rise is determined by those factors which influence maximum systolic pressure. However, baroreceptor activity is not immune to changes due to diastolic pressure, which is related to the fall in pulse pressure. For instance, an increase in TPR would hinder the flow of blood out of the aorta during diastole. With the next heart beat, an additional volume increment would increase AP according to the aortic capacitance. The rate of rise of AP may be increased as well, since the capacitance is not necessarily linear over its whole operating range. Over the next several heart beats, AP would increase to overcome the additional resistance, and

steady-state aortic flow would be reestablished, but the potential for dynamic interactions between TPR and pulse pressure is evident. The significant TPR phase differences, and the large TPR amplitude differences, between the groups of animals in this study provided considerable opportunity for a large variation in pulse pressure between the groups, even in the absence of statistically significant AP differences. For this reason, pulse pressure magnitude is not an unreasonable candidate for the arterial baroreceptor stimulus for the HR changes which dominate the cardiovascular responses of the endurance trained animals to sinusoidal acceleration at the intermediate frequencies. Similarly, consideration must be given to the information content of the pressure pulse waveform itself, which could contain information on the state of the peripheral vasculature sufficient to prompt compensatory HR changes, even in the absence of an altered mean arterial blood pressure.

Caveats.

1) This study was intended as a survey of the cardiovascular frequency response characteristics of endurance trained dogs, compared to sedentary controls. Thus, it was intentionally global in its design and general in its results. The literature (Tables I-III) suggests that the frequencies sampled span the spectrum from the domain

of hormonal control of the vasculature at the low end, up through the neural control of the visceral and then of the skeletal muscle vascular beds, into the regions where neural regulation of heart rate was dominant, and pressure disturbances were passively damped out. As a survey, this effort examined only a few points in each of those frequency domains. There is no a priori reason for measurements made in each of those regions to have similar variances, but the analysis of variance was required to assume such a homogeneity. Thus, the statistical treatment presented here was conservative, and may have ignored training effects which now await more specific investigations and more appropriate statistics.

2) It is important to note that the trends discussed in this report are based on a mathematical manipulation of physiological data to produce somewhat abstract indices of the data's original nature. The amplitude of a waveform's first harmonic component may only approximate the amplitude of the waveform itself; however, it is an objective and consistent reflection of the original. The manual reduction of the polygraph records provided amplitude data (not presented) in which the differences in heart rate excursions were even more evident than in the Fast Fourier Transform (FFT) data. But, without the FFT, the phase information necessary to understand the trained animals' large heart rate variability would not have been available. Thus, the use of mathematical techniques such as

this one may involve a compromise between the knowledge to be gained from them and the information yielded by more traditional methods.

3) An analysis including the higher harmonics of the variables' waveforms would have been more faithful to the actual cardiovascular results. However, it would also have been much more difficult to accomplish. Since statistical comparisons of the second harmonics' amplitudes and phase angles revealed no group differences in any variable, it was decided to limit this investigation to the information contained in the first harmonic component.

4) It will be noted that no mention has been made of the role of the low-pressure, cardiopulmonary baroreceptors in the control of heart rate and peripheral vascular resistance. This predilection with the arterial baroreceptors may seem to ignore the fact that there was as large an acceleration-induced pressure change in the right and left atria (middle panels of Figures 7 and 8, respectively) as is believed to have existed in the aortic arch (Figure 9, middle panel), and presumably in the carotid sinus. When considering the background pressures upon which these dynamic stimuli were imposed (Figures 7-9, top panels), it would seem that the relative stimuli would have been even larger in the atria than in the arteries. However, the low-pressure baroreceptors are usually thought to be involved in the fine control of arterial pressure, and the arterial baroreceptors, in the more

gross regulation (see: Richardson, 1976, pp. 151-155). Accordingly, the role of the high-pressure receptors was emphasized in this study, to the exclusion of their low-pressure counterparts. Notice, though, that the work of Gauer and others (Richardson, p. 152) demonstrates a heart rate response to low-pressure receptor stimulation alone, which may have an analog in the heart rate adjustments noted in this study. Clearly, further investigation of the relative roles of these baroreceptors is indicated.

Recommendations.

The results presented here suggest the direction that future efforts should take to explore these phenomena more fully.

- 1) Selective pharmacological blockades, applied in conjunction with the sinusoidal acceleration stress, could pinpoint the portions of the autonomic nervous system responsible for the differences in cardiovascular regulation due to endurance training.

- 2) The changes in specific vascular beds, following exercise training, could be investigated by selecting the input acceleration frequencies from the appropriate portions of the spectrum, as indicated in the Introduction. As a further aid, flow probes could be placed to measure the blood flow changes in specific beds, such as the viscera, or the skeletal muscles of a hind

limb. This would provide direct information on regional differences in cardiovascular regulation, and on changes in this regulation with training, as well as define more precisely the frequency ranges over which these beds are most active.

3) An acceleration protocol tailored to the specific frequency response characteristics of each animal would reduce the uncertainty inherent in this investigation. This could be done by a preliminary centrifuge experiment, during which the resonant heart rate frequency, for example, could be determined. A simpler way of securing comparable information would require the presence of pacing electrodes on the epicardium. An instantaneous change from a low heart rate to a much higher one induces a pressure disturbance in the arterial blood pressure which reveals its natural frequency. Then, the acceleration protocol could be designed to examine cardiovascular regulation at specific fractions of this frequency.

SUMMARY AND CONCLUSIONS

1) A homogeneous group of dogs, as assessed by heart rate measurements at rest and during submaximal exercise on a treadmill, was randomly divided into two subgroups.

2) One subgroup was endurance trained for six weeks by means of a treadmill running program. The other was left untrained, as sedentary controls.

3) After six weeks of endurance training, there was a significant difference in the cardiovascular trained states of the two groups, as assessed by heart rate responses to submaximal exercise on the treadmill.

4) In response to a protocol of sinusoidal acceleration on a modified centrifuge, both groups of dogs maintained and regulated aortic blood pressure to comparable degrees.

5) The untrained dogs relied largely on peripheral resistance mechanisms to regulate blood pressure at acceleration frequencies of 0.008 to 0.035 Hz, and then on heart rate adjustments at higher frequencies.

6) In contrast to the control animals, the endurance trained dogs relied primarily on peripheral resistance mechanisms to regulate blood pressure only at 0.008 Hz. Heart rate adjustments were more dominant from 0.016 to 0.035 Hz.

7) The maximum peripheral resistance responses to the blood pressure oscillations were delayed in the trained dogs compared to those in the untrained dogs.

8) Endurance training was associated with a sluggish peripheral vascular response to blood pressure disturbances with periods of 40-60 seconds. This was compensated for by large amplitude heart rate variations. As a result, aortic arch blood pressure was maintained at similar levels in both the untrained and the aerobically conditioned animals.

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IV. CHANGES IN PEAK LEFT VENTRICULAR WALL
STRESS IN NORMAL AND CARDIAC DENERVATED
CANINES DURING SINUSOIDAL ACCELERATION

SUMMARY OF DISSERTATION

BENJAMIN S. KELLEY

1983

ABSTRACT

A comparison of changes in peak left ventricular wall stress in normal and cardiac denervated canines during sinusoidal acceleration was made to determine the effects of extrinsic cardiac innervation on wall stress. Blood pressure oscillations in tranquilized chronically instrumented canines were produced via changes in central blood volume created by sinusoidally varying spinal axis acceleration ($\pm 2G$ at 0.004 to 0.25 Hz). Left ventricular pressure and three dimensions (major and minor axis and wall thickness) were measured and used to calculate peak wall stresses employing a prolate ellipsoid computer model. The largest acceleration-induced peak wall stresses for six normal and six cardiac denervated animals were found to occur at a frequency of 0.025 Hz. The smallest acceleration induced peak wall stress occurred at frequencies below 0.008 Hz in the normal animals and below 0.014 Hz in the cardiac denervated animals. The time of occurrence of these extreme stresses, within the acceleration cycle, corresponded more to the peak gradient of acceleration than to the peak acceleration force itself, implying a closer correlation with sudden volume shifts of blood than with extremes in hydrostatic forces. Wall stress values for the normal animals were lower ($P < 0.05$) than those of the cardiac denervated animals for acceleration frequencies below 0.02 Hz. Evidence of neural mediation was also found from significant differences, between the two groups in the time relationship of maximum and minimum peak wall stresses for frequencies above 0.03 Hz.

left ventricular wall stress

ellipsoidal model

sinusoidal acceleration

cardiac denervation

TABLE OF NOMENCLATURE

G	Magnitude of acceleration due to gravity, 9.81 m/sec^2
w	Circular frequency, radians per second
R	Radius, meters
t	Time, seconds
θ	Circumferential coordinate
ϕ	Longitudinal coordinate
S	Stress resultant gm/cm
σ	Wall stress gm/cm^2
r_1	Primary (circumferential) radius of curvature, mm
r_2	Secondary (longitudinal) radius of curvature, mm

INTRODUCTION AND BACKGROUND

The circulatory system is maintained in a state of dynamic equilibrium by a number of complex and sensitive cardiac and vascular control mechanisms that act to minimize systemic pressure, flow, and volume disturbances. Proper and effective cardiovascular control is therefore essential to the preservation of physiological integrity under normal, diseased and varied environmental conditions.

Some of the most common non-invasive stimuli seen by the cardiovascular system are due to transient acceleratory and gravitational loadings such as those associated with normal daily activity, exercise, or severe occupational environments. These stimuli are capable of producing significant arterial and venous pressure and flow change fluctuations (1,3,6) that may severely challenge cardiovascular regulation.

The degree to which the control network is able to minimize these transient disturbances is determined by the dynamic response characteristics of the cardiovascular system, in general, and the integrated function of the individual cardiac and vascular control mechanisms, in particular.

Earlier studies of cardiovascular regulation indicate that the dynamic frequency response of these mechanisms is limited primarily to the frequency range below 1.0 Hz (12,15,21,25,27). The majority of these studies, however, examined the response of specific control mechanisms to invasively applied local stimuli, using anesthetized animal preparations. Consequently, the application of the dynamic frequency response of cardiovascular regulation and control mechanisms

in unanesthetized animals exposed to a more natural, non-invasive stimulus, such as the global pressure, flow, and volume disturbances associated with whole-body gravitational or acceleration-induced forces, has yet to be totally described.

More recently, investigators have begun to utilize more global stimuli (4,9,16,19). While attempts have been made to assess the contributions of specific physiological variables (mean pressures, flows, volumes, and resistances) to global whole-body acceleration-induced disturbances, no previous attempt has ever been made to investigate the mechanical disturbances to the myocardium itself, in particular, the fluctuations in left ventricular wall stresses. Disturbances of ventricular pressures and dimensions stimulate cardiac compensatory reflex mechanisms and thus altering left ventricular wall stresses. However, the dynamic time relationship of left ventricular wall stresses to oscillatory fluctuations in the essential cardiovascular parameters (pressures, flows, and resistances) has yet to be addressed.

Efforts to determine stresses within the left ventricular wall have utilized numerous techniques. Most of the earlier attempts employed either a method of directly measuring the stresses (17) or by using simplified geometric models (5,8,18,24,29). More recently however, investigators have begun to use various forms of the finite element method for the estimation of ventricular wall stresses (7,10,11,20). Current technical methods available for the determination of ventricular geometry and material properties however, do not allow for the complete utilization of the finite element method for the determination of ventricular wall stresses. The ease of employing idealized geometry models thus continues to make these

models very useful.

The specific objective of the present investigation is to quantify the active (normal) and passive (cardiac denervated) wall stress responses of the left ventricle to time-dependent acceleration loadings and to place these stress responses in perspective with frequency response data of other cardiovascular parameters (pressures, flows and resistances). A comparison of wall stress responses will also indicate the influence of extrinsic cardiac innervation on wall stress. The present study examines the time relationship of peak left ventricular circumferential and longitudinal wall stress over each cardiac cycle in unanesthetized (but tranquilized), chronically instrumented dogs exposed to sinusoidal, whole-body, spinal-axis acceleration ($\pm 2G_z$) at ten discrete acceleration frequencies between 0.004 and 0.25 Hz. Wall stresses were obtained by utilizing a prolate ellipsoidal model to represent the left ventricular geometry.

METHODS

Adult male and female mongrel dogs weighing between 13 and 24.5 kg were used as experimental subjects. The principles of laboratory care outlined by the National Society for Medical Research were rigorously observed in all phases of this work. Before surgery, each dog was anesthetized with sodium pentobarbitol (20 mg/kg) and placed on artificial positive pressure respiration. The heart was then exposed by cutting the pericardium longitudinally after a left thoracotomy had been performed through the fourth intercostal space. The cardiac denervation method of Randall et al (22) was performed at this time on the cardiac denervated animals. The efficacy of the denervation was confirmed prior to chest closure by demonstrating the

complete absence of change in atrial and ventricular contractile force (determined from acutely placed Walton-Brodie strain gauge arches or by visual inspection) and heart rate during stimulation of the left and right thoracic vagi and left and right stellate ganglion.

In order to measure left ventricular dimensions in both groups of animals, a pair of five mm diameter ultrasonic dimension transducers (fabricated using type LT22 Lead Titanate Zirconate) were positioned to provide epicardial major and minor axis diameters of the left ventricle, following the method of Rankin et al (23). The left ventricular wall thickness was measured by a one mm diameter crystal tunneled to the endocardial surface of the anterior wall and a three mm diameter crystal sutured to the overlying epicardium. For measuring left ventricular pressure, a pressure transducer (Konigsberg Instruments) was inserted one cm into the left ventricle through a stab incision in the apical dimple.

The connecting leads from the chronic instrumentation exited the thorax at the third intercostal space and were stored in a subcutaneous dacron pouch placed between the scapulae. Due to the controversy surrounding the influences of a surgically closed pericardium on left ventricular mechanics (19) the pericardium was left open in the present study.

The chest was then closed after the completion of all of the surgical procedures, and the dog was placed in a recovery kennel for several hours. Each animal was allowed at least three weeks of postoperative recovery before centrifuge studies were begun. On the day of the centrifuge experiment, the dog was tranquilized with an intramuscular injection of Innovar Vet (0.075 cc/kg). A

piezoelectric, manometer-tipped, pressure gauge catheter (Millar) was placed in the left ventricle via a small branch of a main femoral artery for use in calibrating the implanted pressure transducer. Supplemental doses of Innovar Vet (0.5 ml/20 kg) were administered to maintain the animal in a lightly tranquilized state.

Low frequency, acceleration induced stresses were provided by a fifty foot (15.2 m) diameter centrifuge (Figure 1). The animal restraint couch and associated instrumentation were mounted on the arm of the centrifuge on a platform capable of being independently counter-rotated, so that its center of rotation was approximately at heart level. With the large centrifuge rotating at a speed required to produce a radial 2G acceleration, constant counter rotation of the animal platform resulted in sinusoidal acceleration along the animal's spinal axis ($\pm 2G_z$) at various frequencies. The time relationship of the G_z acceleration loading is given as

$$G_z = [-w_R^2 R \cos(w_R t) - (w_R + w_r)^2 r] \quad (1)$$

where R is the distance from the center of rotation of the large centrifuge to the center of rotation of the platform, r is the distance from the center of rotation of the platform to an arbitrary point along the spinal axis of the animal, w_R is the rotational speed of the large centrifuge, and w_r is the rotational speed of the platform (14).

After the placement and calibration of all of the instrumentation on the day of the experiment, the animal was secured in the restraint couch mounted on the rotatable platform. The test sequence consisted of $\pm 2G$ sinusoidally varying acceleration at discrete frequencies ranging from 0.004 to 0.25 Hz. Each frequency test lasted approximately three to four minutes. The acceleration frequencies

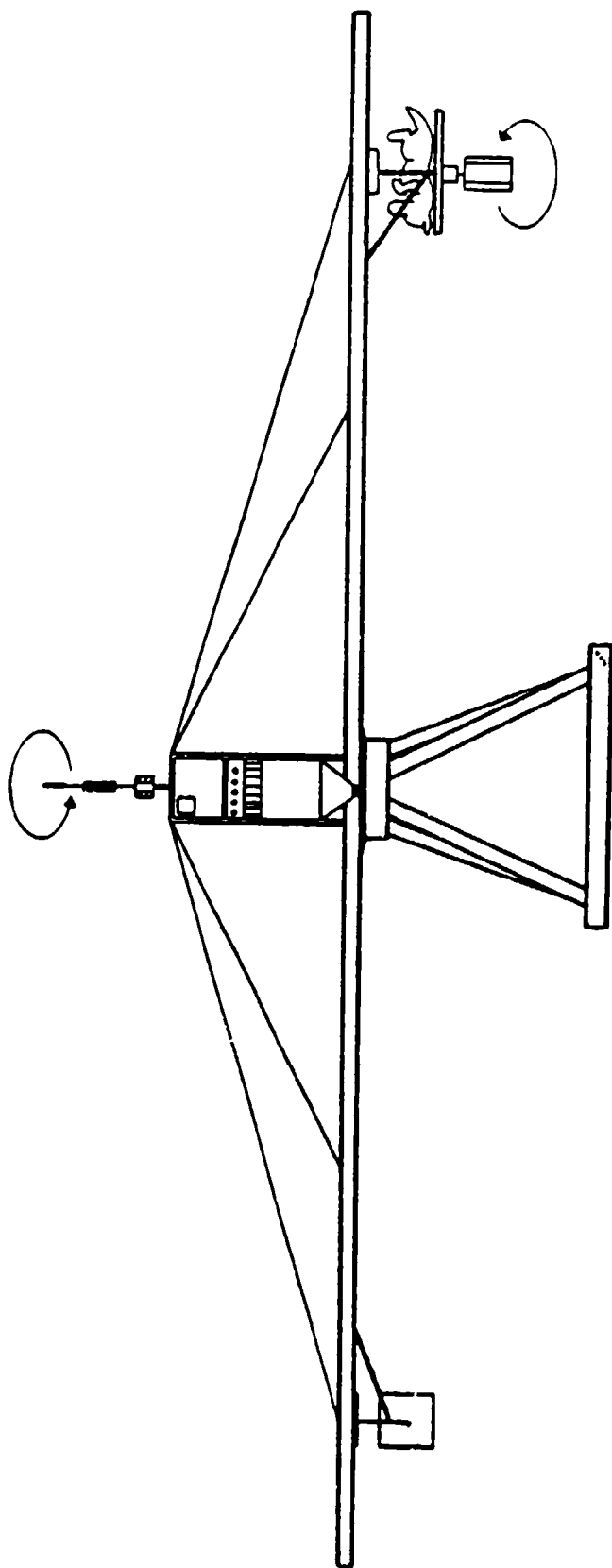


FIGURE 1
Large animal centrifuge with rotating platform.

were applied sequentially, starting at the lowest frequency and then moving to the next higher frequency without stopping the centrifuge between frequencies. Following the completion of the highest acceleration frequency, the centrifuge was halted and recovery values for each variable were immediately obtained.

All physiological signals from the experimental animal, and spinal axis (G_z) acceleration were transmitted through two sets of slip rings to a remote location where they were monitored. A continuous on-line magnetic tape record and a strip-chart record were made of the variables.

ANALYSIS

The data sampling and stress analysis were carried out on a DEC PDP 11/34 computer system. A digital sampling frequency of 161 Hz was used for all five of the measured variables (spinal axis acceleration, left ventricular pressure major ventricular axis, minor ventricular axis, circumferential wall thickness). User written BASIC computer programs were employed for the evaluation of the left ventricular dynamic geometry and loadings, and consequently, the determination of peak wall stresses and their time relation to the sinusoidal acceleration.

A complete derivation of the equations required to make the stress calculations would be a lengthy procedure and thus only the basic assumptions and formulations are presented here. The following general assumptions were employed in the derivation of the wall stress equations.

- A. The left ventricular wall was linearly elastic and behaves as an isotropic and homogeneous medium.
- B. Throughout the cardiac cycle, the geometry of the left

ventricle can be approximated by a prolate ellipsoidal shell of revolution (Figure 2).

- C. Only the solid mechanics aspects of the left ventricular wall were considered. No attempt was made to include the inertia or acceleration effects of the heart muscle or blood, or the effects of fluid shear forces. The intraventricular pressure acting normal to the endocardium was the only load on the left ventricle.
- D. As a consequence of the assumed symmetry of deformation, bending moments and shear forces were neglected and thus the myocardium was held in a state of equilibrium by the circumferential and longitudinal stress components acting within.
- E. The problem was considered to be quasistatic where instantaneous measurements of geometry and pressure were utilized in a static analysis.

A typical wall shell element shown in Figure 3, depicting the middle surface, was cut out by two meridians and two parallel circles, each infinitely close together. Only circumferential (S_θ) and longitudinal (S_ϕ) stress resultants are shown since shear forces and bending moments were not considered. By summing the forces parallel to the meridians and parallel circles, and perpendicular to the middle surfaces, equations of equilibrium may be obtained as

$$\sigma_\theta = \frac{Pr_2}{h} \frac{2r_1 - r_2}{2r_1} \quad (2)$$

$$\sigma_\phi = \frac{1}{2h} Pr_2 \quad (3)$$

where σ_θ and σ_ϕ are the circumferential and longitudinal stress components respectively. P is the measured left ventricular pressure, h is the wall thickness at a point of interest, and r_1 and r_2 are the principal radii of curvature.

The ventricular wall thickness at any location can be determined by solving the equation for the line perpendicular to the wall at that location, simultaneously with the elliptic equations for the inner and

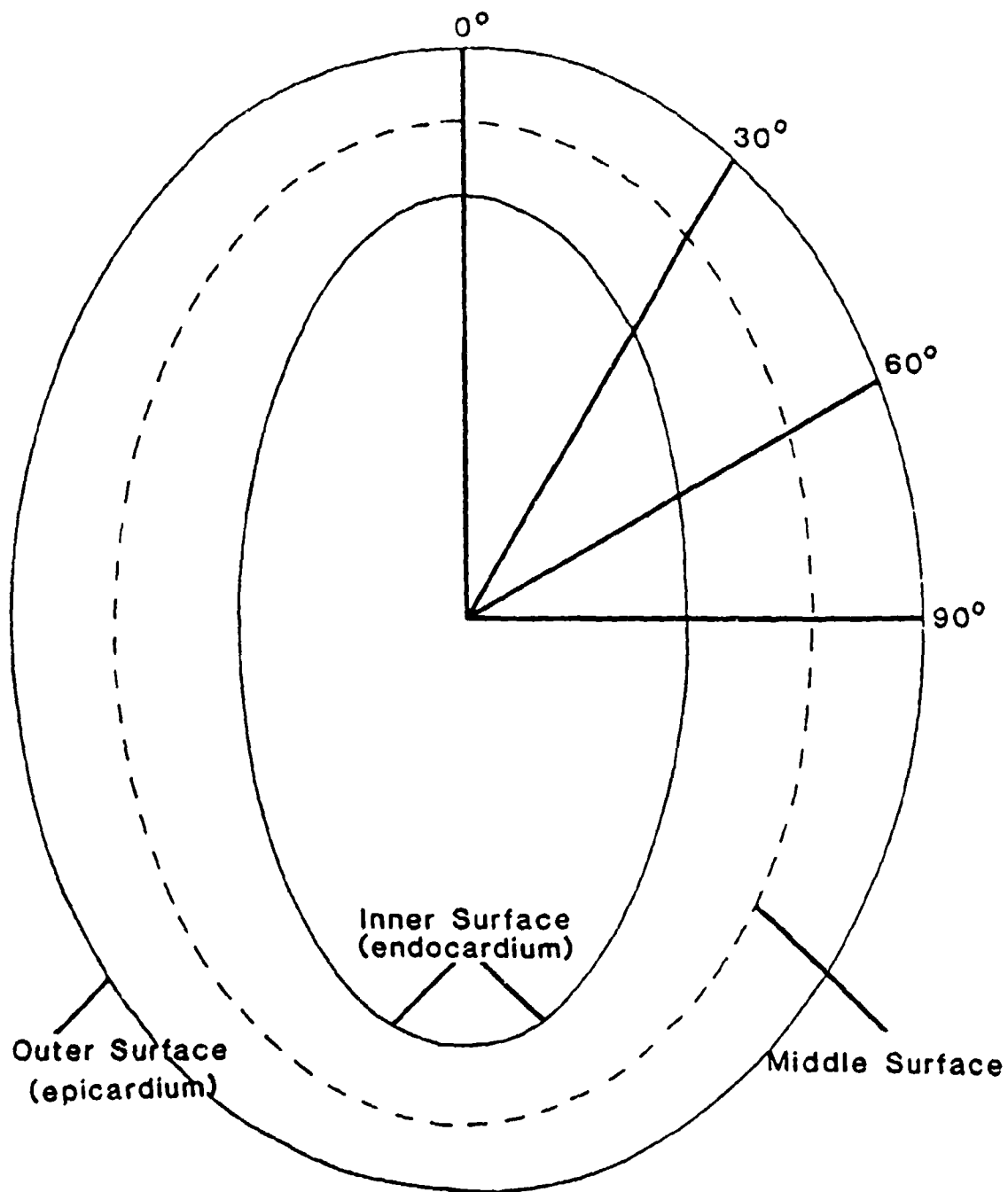


FIGURE 2
Prolate ellipsoid model of left ventricular geometry used for stress analysis.

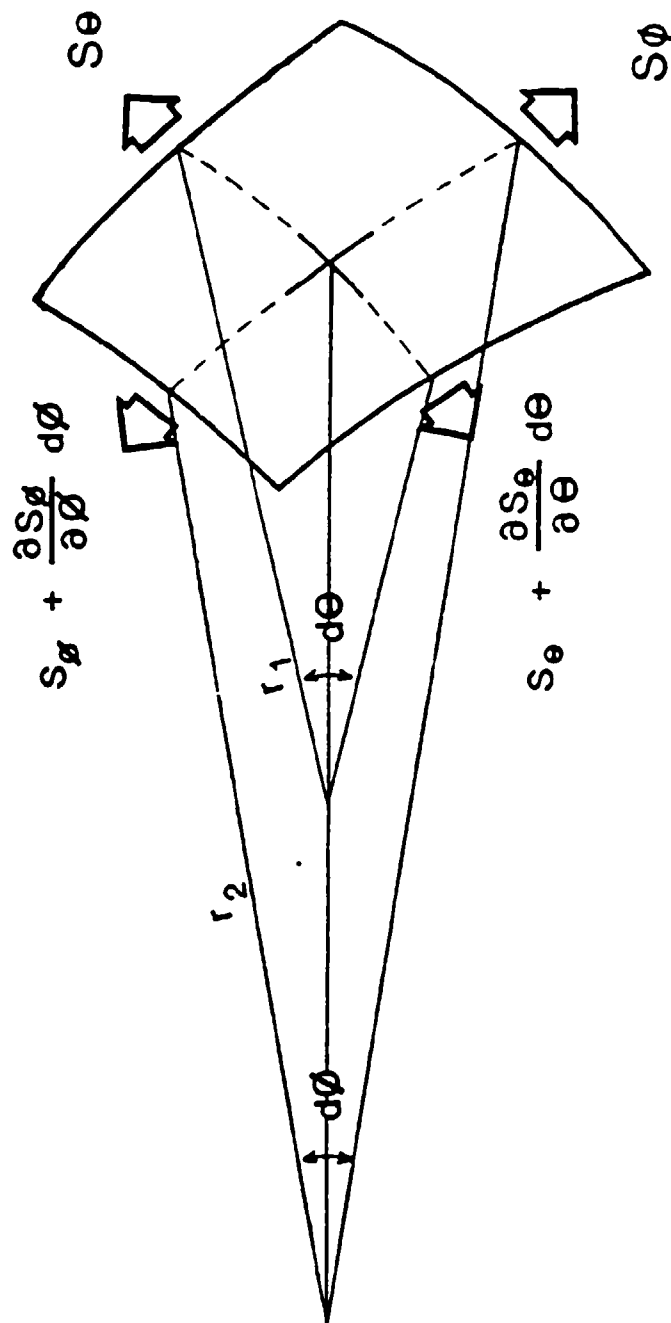


FIGURE 3
Shell element cut from ventricular wall (thickness not indicated) with principal radii of curvature r_1 and r_2 and rotated through infinitely small angles $d\theta$ and $d\phi$.

outer surfaces and utilizing the distance formula. The wall thickness at the apex and base was assumed to be 55% of the measured equatorial wall thickness (23). The resulting expression for the wall thickness can be written as

$$h = ((x_o - x_i)^2 + (y_o - y_i)^2)^{1/2} \quad (4)$$

where x_o , x_i and y_o , y_i are determined from solution of the simultaneous equations mentioned above.

RESULTS

Due to the complex nature of the wall stress analysis of the beating heart and the additional complications resulting from the time-dependent acceleration loading, it will be necessary to initially define the stress terms in relation to the cardiac cycle and then the acceleration cycle. The following terms will apply to either the longitudinal or circumferential wall stress at each of the four locations of the left ventricular wall (0° , 30° , 60° , 90° ; Figure 2) being examined:

- a) Peak stress - the greatest stress value occurring during a cardiac cycle.
- b) Maximum peak stress - the largest value of peak stress occurring during an acceleration cycle.
- c) Minimum peak stress - the smallest value of peak stress occurring during an acceleration cycle.
- d) Mean peak stress - the average value of peak stress occurring over an acceleration cycle.
- d) Delta peak stress - the difference between maximum and minimum peak stresses during an acceleration cycle.

The peak longitudinal and circumferential left ventricular wall stresses were calculated in both the normal and cardiac denervated dogs over the acceleration frequency range, using the prolate ellipsoid model shown in Figure 2. Stresses were calculated at 0° (apex or base due to symmetry), 30° , 60° , and 90° (equator). Responses were averaged when more than one acceleration cycle was analyzed so that an "equivalent" acceleration cycle response was obtained.

There were significant differences between the groups in their stress responses at the lower acceleration frequencies (Table 1) and significant differences in the time relation angles (relating time of maximum and minimum peak stresses to input acceleration) at the middle

TABLE 1

Statistical comparison for normal versus cardiac denervated grouped means of mean, maximum, and minimum peak longitudinal (\emptyset) and circumferential (\emptyset) wall stress for the three lowest acceleration bins employing Newman-Keuls Multiple Range significance test.

99 percent confidence interval -- ** -- $p < 0.01$

95 percent confidence interval -- * -- $p < 0.05$

Blanks denote less than 95 percent confidence interval.

Non-Normalized

Acceleration Frequency (Hz)	0.004 to 0.008 \emptyset \emptyset	0.008 to 0.014 \emptyset \emptyset	0.014 to 0.020 \emptyset \emptyset
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Mean peak left ventricular wall stress

00	*	*	*	*
300	*		**	
600				
900				

Maximum peak left ventricular wall stress

00	**	**	*	*
300	*	**		**
600				
900				

Minimum peak left ventricular wall stress

00	*	*	**	**	*	*
300	*	**	**	**	*	*
600	*	*	**	**	*	
900				**		

and high acceleration frequencies.

In general, peak left ventricular wall stress, within the cardiac cycle, normally occurred early in systole, simultaneously with peak left ventricular pressure in both the normal and cardiac denervated dogs. While peak left ventricular pressure is a good indicator of the magnitude as well as the time of occurrence of peak wall stress within the cardiac cycle during control conditions, the largest peak left ventricular pressure was not necessarily a good indicator of the largest wall stress and its location within and acceleration cycle. Changes in left ventricular dimensions over cardiac cycles in a control state oscillate around mean dimensions. During sinusoidal acceleration, however, the average values about which ventricular dimensions oscillate are continually changing, being a function of both the magnitude of the acceleration and the particular acceleration frequency. With dimensions changing in such a manner, the location of the largest value of left ventricular pressure during an acceleration cycle did not necessarily constitute the location the largest value of the left ventricular wall stress.

Of all of the acceleration frequencies used in this study, the largest acceleration-induced peak left ventricular wall stress in both the normal (390 gm/cm^2) and cardiac denervated (398 gm/cm^2) dogs, occurred at an acceleration frequency of 0.025 Hz and in the circumferential direction at the equator (90°) of the left ventricle (Figure 4 and 5). However, the time of occurrence of these largest peak stresses within the acceleration cycle was not the same for the two groups of animals. For the normal dogs, the largest peak stress to the myocardium during the $\pm 2G_z$ acceleration cycle occurred at a time when the animal was exposed to only $0.1 G_z$ (time relation angle

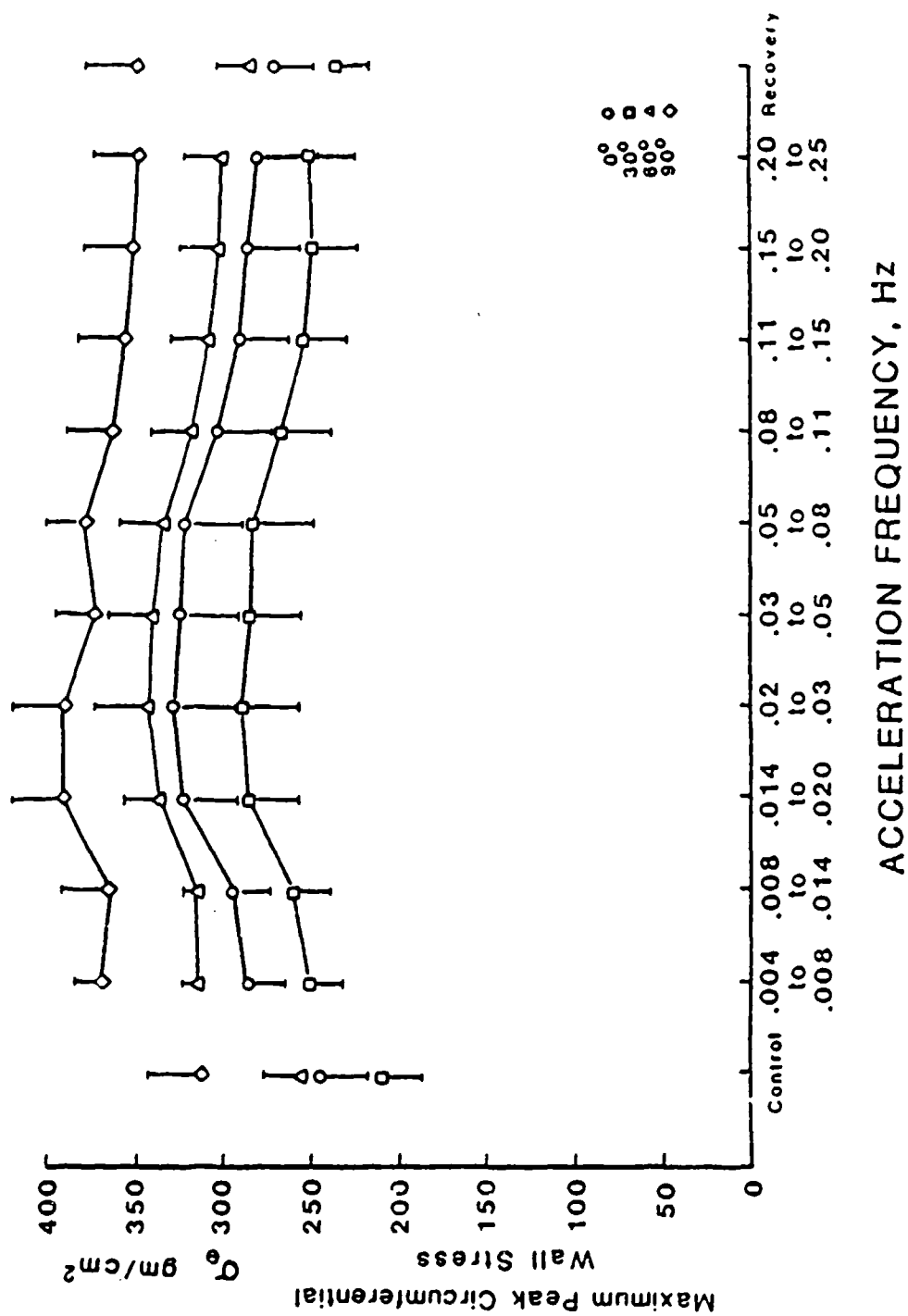


FIGURE 4
Maximum peak left ventricular circumferential wall stress (gm/cm²) versus acceleration frequency (Hz) in normal animals.

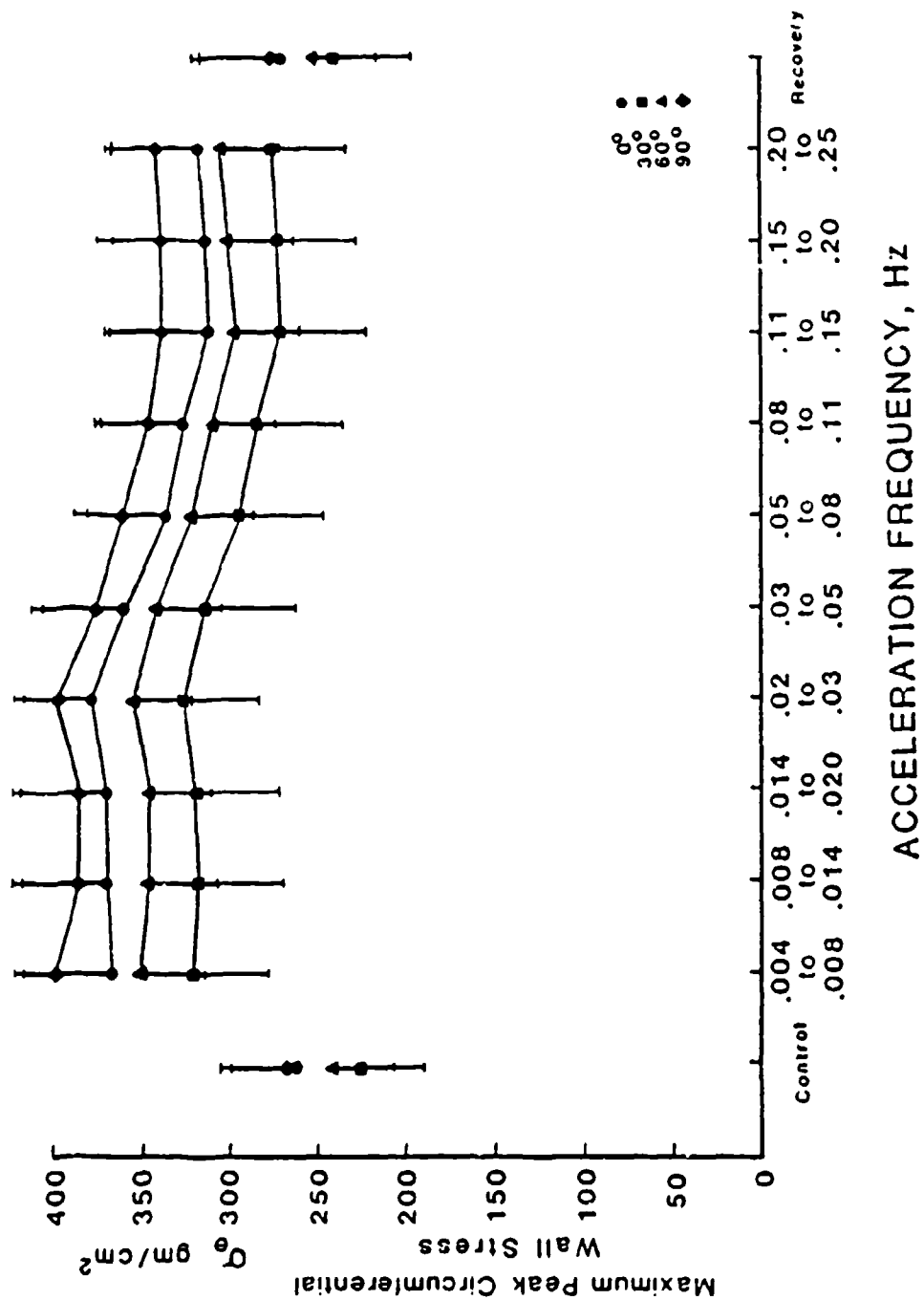


FIGURE 5
Maximum peak left ventricular circumferential wall stress (gm/cm²) versus acceleration frequency (Hz) in cardiac denervated animals.

of 178° , Figure 6). This time in the acceleration cycle corresponded to blood being shifted toward the head, after having been pooled in the lower body during the $+2G_z$ portion of the cycle (i.e. $-dG/dt$). For the cardiac denervated animals, maximum stress to the left ventricle occurred during $+1.5G_z$, which also corresponds to blood being shifted toward the head following the $+2G_z$ pooling in the lower body, but at a much earlier time in the acceleration cycle than that for the normal dogs. This situation corresponds to a time relation angle of 118° for the 0.025 Hz acceleration frequency (Figure 7).

The smallest acceleration-induced peak left ventricular wall stress, observed over the entire acceleration frequency range, occurred at frequencies below 0.008 Hz for the normal dogs (109 gm/cm^2), and between 0.02 and 0.03 Hz for the cardiac denervated dogs (150 gm/cm^2). These stresses were well below control values in both groups of animals. For both groups, the smallest wall stress occurred in the longitudinal direction at 30° (with respect to the base or apex, Figure 8 and 9). Like the largest peak stress case, the smallest peak wall stress for the two groups occurred at different times in the acceleration cycle. The smallest stress for the normal dogs occurred when the animal was exposed to $1.7G_z$ (time relation angle of 58° , Figure 6) corresponding to a time in the acceleration cycle when blood was shifting toward and pooling in the lower body, after having been pooled in the upper body during the $-2G_z$ portion of the cycle. The smallest peak stress for the cardiac denervated dogs occurred when the animal was exposed to $0.2G_z$ (time relation angle of 5° , Figure 7) corresponding to a time in the acceleration cycle when blood was being shifted toward the lower body, after having been

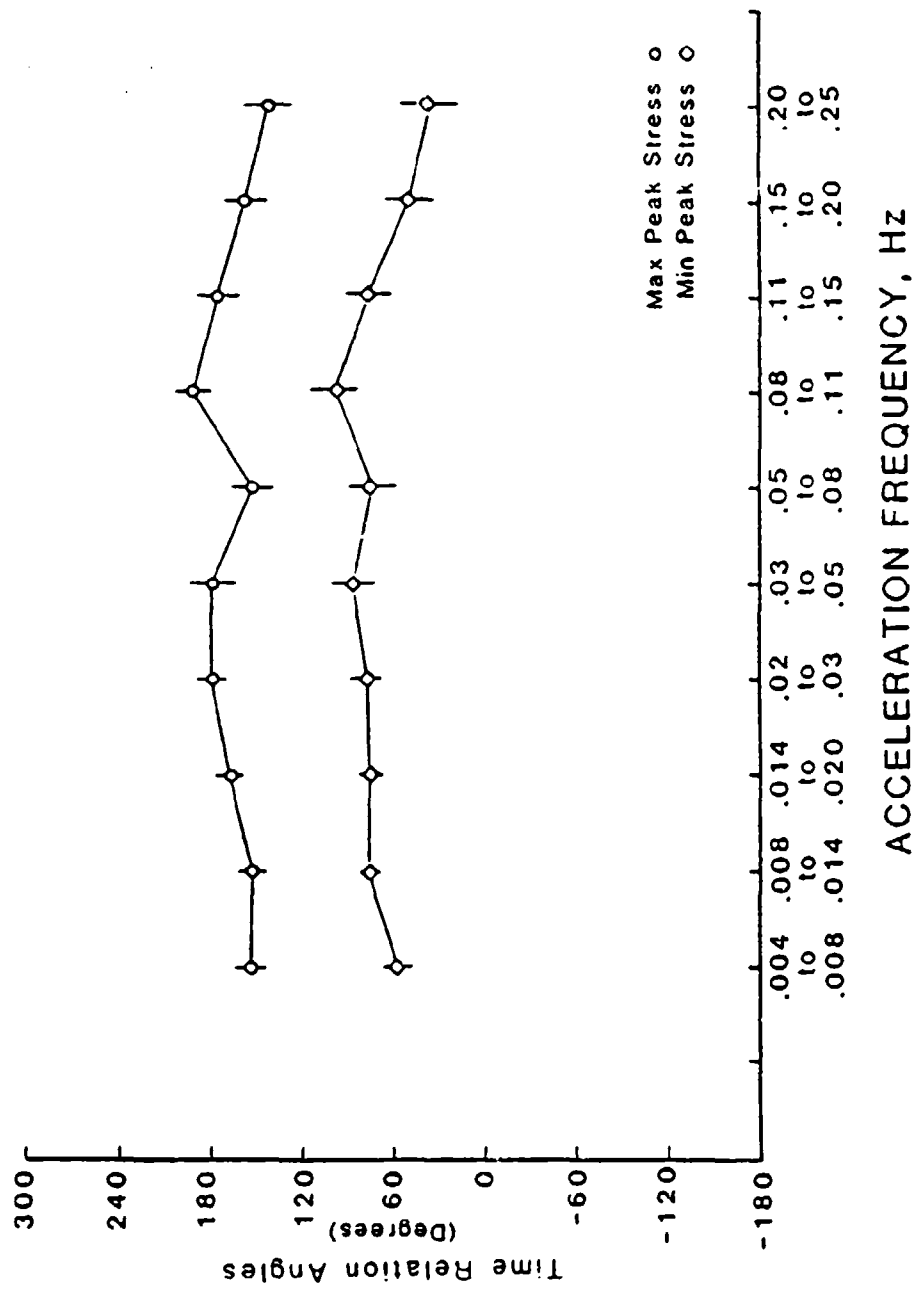


FIGURE 6
Time relation angles (degrees) for maximum (circle) and minimum (diamond) peak wall stresses versus acceleration frequency (Hz) in normal animals (open symbols).

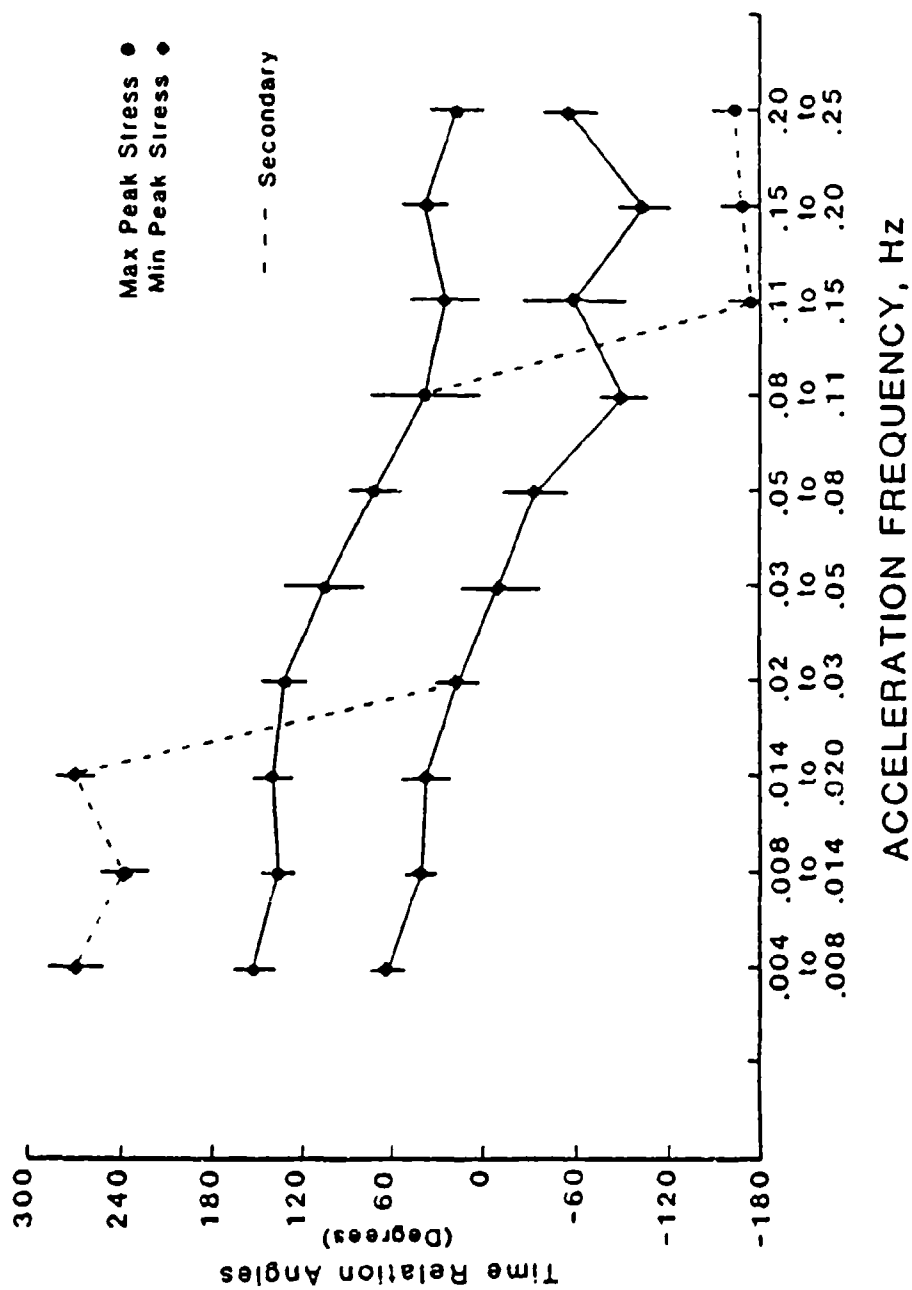


FIGURE 7
Time relation angles (degrees) for maximum (circle) and minimum (diamond) peak wall stresses versus acceleration frequency (Hz) in cardiac denervated animals (closed symbols).

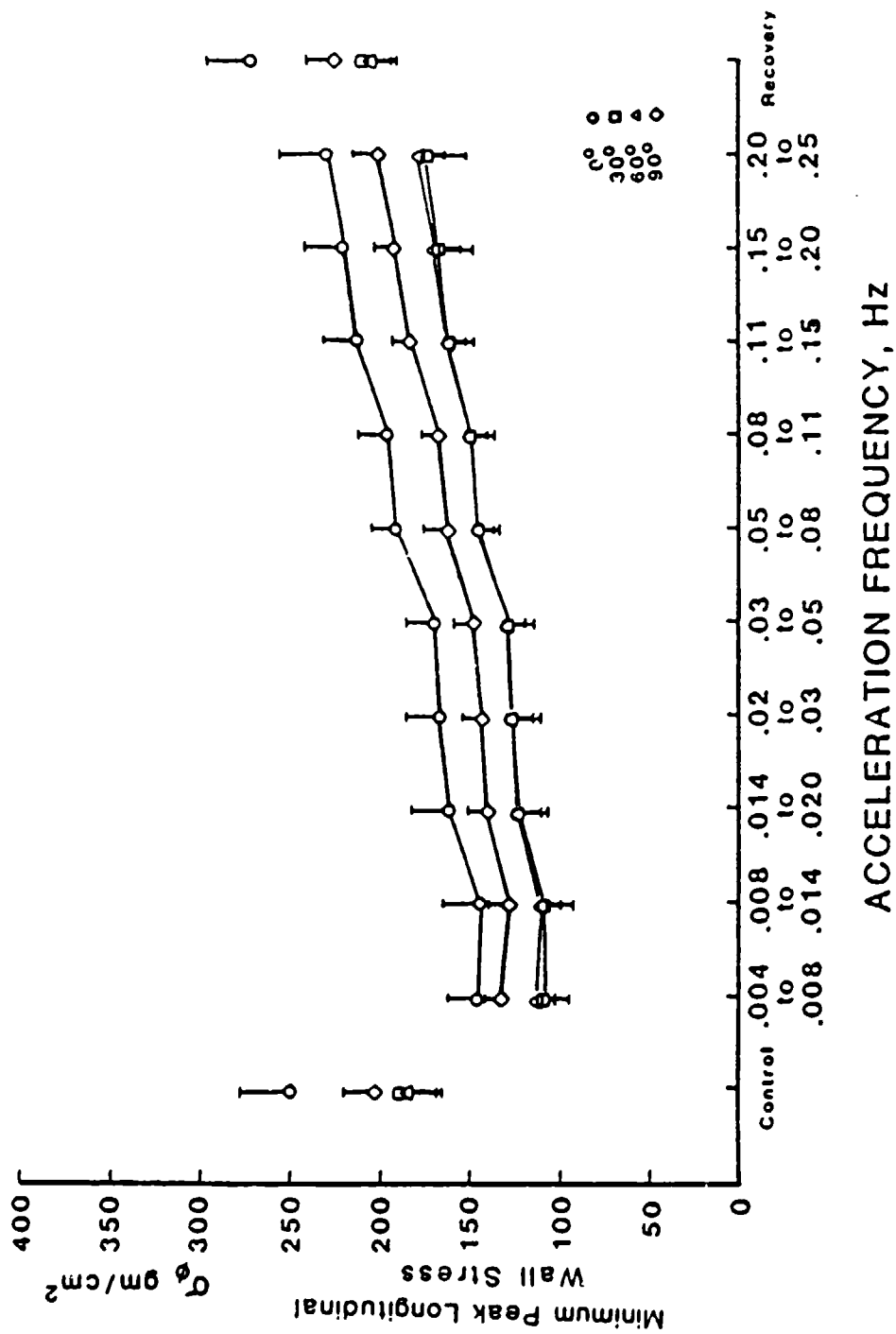


FIGURE 8
Minimum peak left ventricular longitudinal wall stress (gm/cm²) versus acceleration frequency (Hz) in normal animals.

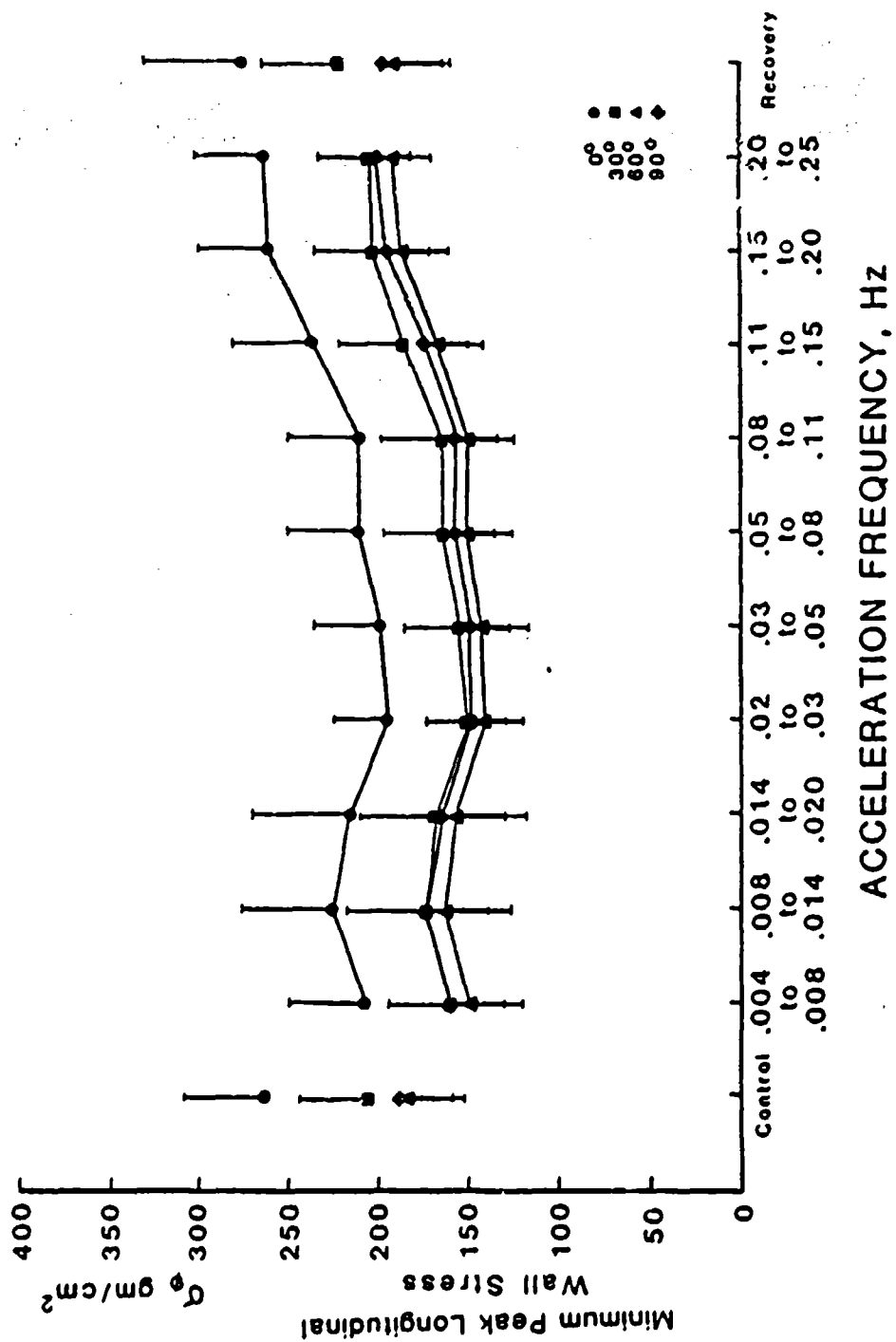


FIGURE 9
Minimum peak left ventricular longitudinal wall stress (gm/cm²) versus acceleration frequency (Hz) in cardiac denervated animals.

pooled in the head during the $-2G_2$ portion of the cycle (i.e. $+dG/dt$).

DISCUSSION

A comparison of left ventricular peak wall stress, for the two groups, at each acceleration frequency indicated that wall stresses for the cardiac denervated group of animals was significantly higher than those of the normal group for frequencies below 0.02 Hz. The significant differences between the two groups occurred at all four locations (0° , 30° , 60° , and 90°) of the left ventricle examined (Table 1). It is reasonable to assume that these differences in the responses between the normal and cardiac denervated data are due to, or at least relate to, the lack of cardiac neural feedback control in the denervated group. The average twenty percent lower peak wall stresses in the normal animals for frequencies below the 0.02 Hz value, when compared to the cardiac denervated group, is indicative of the relative magnitude of this neurally-mediated activity (Figure 10).

It is clear from the data that the largest and smallest peak wall stresses occurred at a time in the acceleration cycle when the animal's heart and cardiovascular system were not exposed to the largest or smallest acceleration forces, and thus to the largest or smallest hydrostatic forces. The explanation for this difference, however, is not as clear. One possible cause is that the changes in ventricular wall stress during the 0.025 Hz acceleration cycle are more directly related to the blood volume shifts resulting from the acceleration-induced hydrostatic forces than the levels of the forces themselves. Direct evidence quantifying blood volume changes during relatively rapidly changing hydrostatic forces is lacking because of the experimental difficulties associated with such volume measurements. Indirect evidence is clouded by the complicated nature

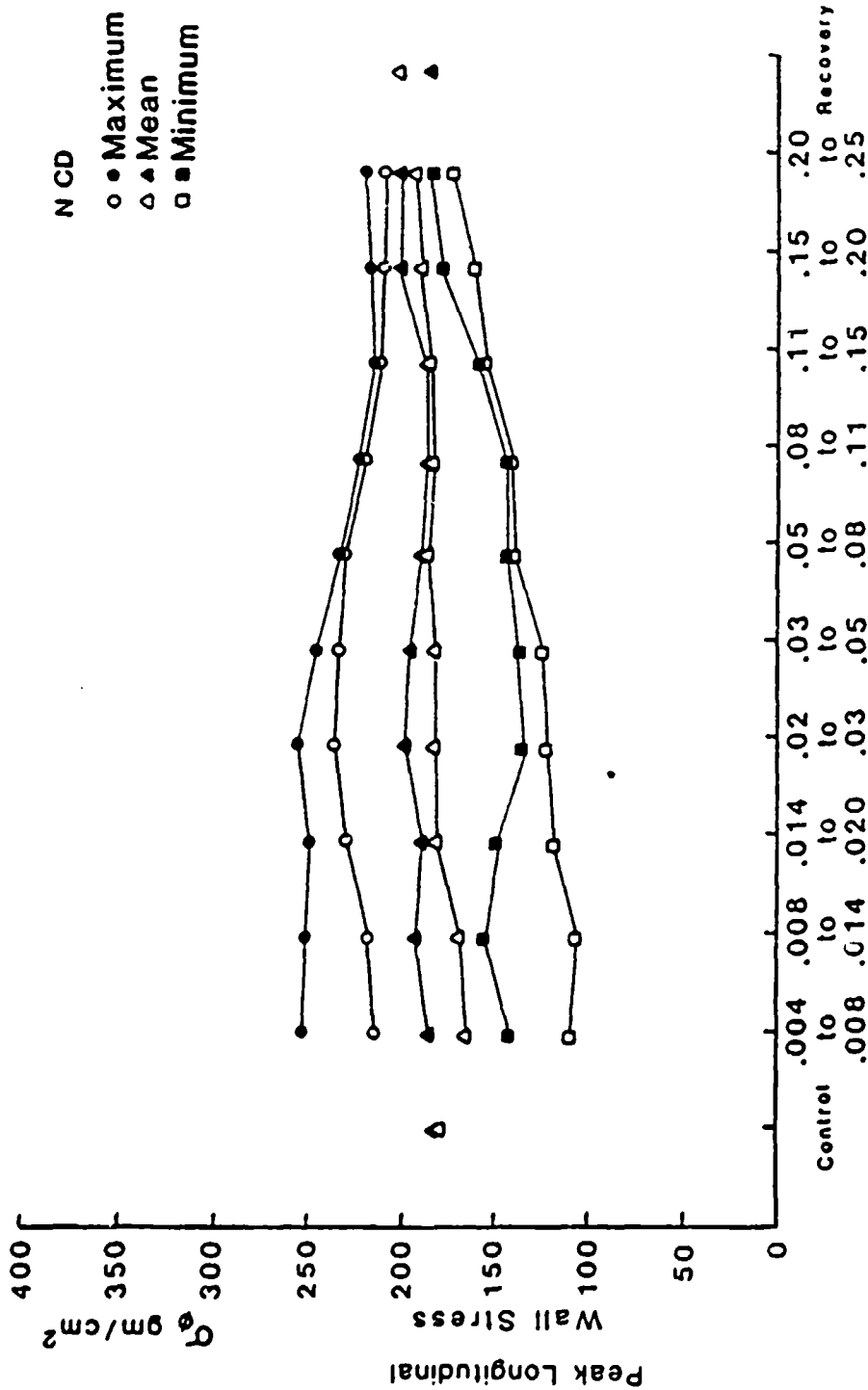


FIGURE 10
Illustration of 60° peak longitudinal wall stresses versus acceleration frequency demonstrating significant differences below 0.02 Hz in maximum (circle), mean (triangle), and minimum (square) peak wall stress responses in normal (open symbols) and cardiac denervated (closed symbols) dogs.

of the coupling between the heart and vasculature, the non-Newtonian viscous properties of the blood and the relative blood storage capacity of the upper and lower body segments. However, it appears that left ventricular wall stress, in general, increases because of the engorgement of blood to the heart and decreases with its withdrawal. Because of the nature of the compliance and resistance of the vasculature and the relative volume capacity of the upper and lower venous sides of the circulation, the volume shifts are almost of a "sloshing" nature, and therefore more closely aligned with the gradient of the G_z force (and the corresponding gradient of the hydrostatic force) than the actual levels of the hydrostatic force associated with the peak + or - $2G_z$ loadings.

The general features of the stress response data in the present study are in good agreement with the results of previous investigations which have used animals to investigate either the overall global or specific local press-flow responses. The agreement is particularly good with respect to the identification of a common corner or resonant frequency for normal, cardiac denervated or pharmacologically blocked animals.

Because afterload, and consequently left ventricular wall stress, are related to both arterial pressure and peripheral vascular resistance, an effort will be made to compare the data of the present study to the data of previous investigations which have explored the frequency responses of these pressures and resistances. An attempt will then be made to put the stress response data in perspective with the levels and the time relation data of disturbance-induced arterial pressure and peripheral vascular resistance changes of previous

investigations.

The peak wall stress responses in the normal dogs reported in this study are similar in nature to the aortic pressure measurements of Knapp et al (14) made in normal dogs exposed to the same acceleration input. Like the maximum and mean peak wall stress response in the normal dogs, they found a similar response for the magnitude of maximum and mean aortic pressure, i.e. nearly invariant with acceleration frequency with only a slight rise in maximum aortic pressure at the mid acceleration frequencies. They, likewise, found minimum aortic pressure to gradually increase with increasing acceleration frequency above 0.021 Hz, as minimum peak wall stress did in this study.

The general characteristics of the excursions of peak left ventricular wall stress (delta peak wall stress, Figures 11 and 12) have an almost identical relationship with acceleration frequency as those found in excursions of peripheral vascular resistance reported by Knapp (13) in normal and cardiac denervated dogs exposed to the same type of acceleration stress. In both groups of animals, he found increasing excursions in total peripheral resistance for acceleration frequencies below 0.021 Hz, followed by a rapid decrease in excursions for acceleration frequencies up to 0.25 Hz. The same type of response was found for delta peak wall stresses in the present study.

A comparison of the qualitative aspects of the dynamic response of peak wall stress to the data from the previous studies cited above, suggests that there exists a functional relationship across the frequency range between acceleration-induced magnitudes of aortic pressure. The acceleration-induced aortic pressure excursions do not correlate as well with wall stress excursions because of slight

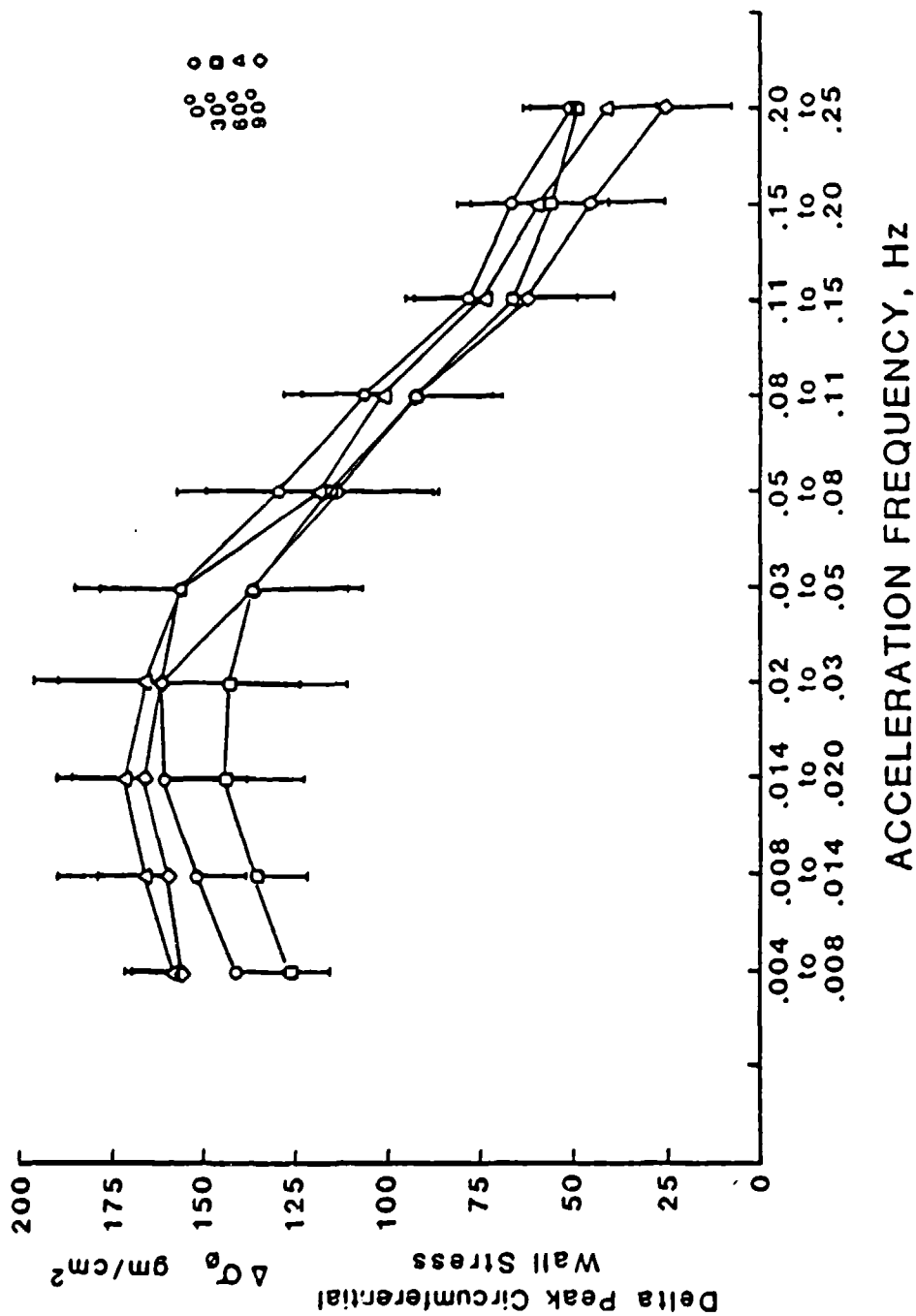


FIGURE 11
Delta (maximum - minimum) peak left ventricular circumferential wall stress (gm/cm^2) versus acceleration frequency (Hz) in normal animals.

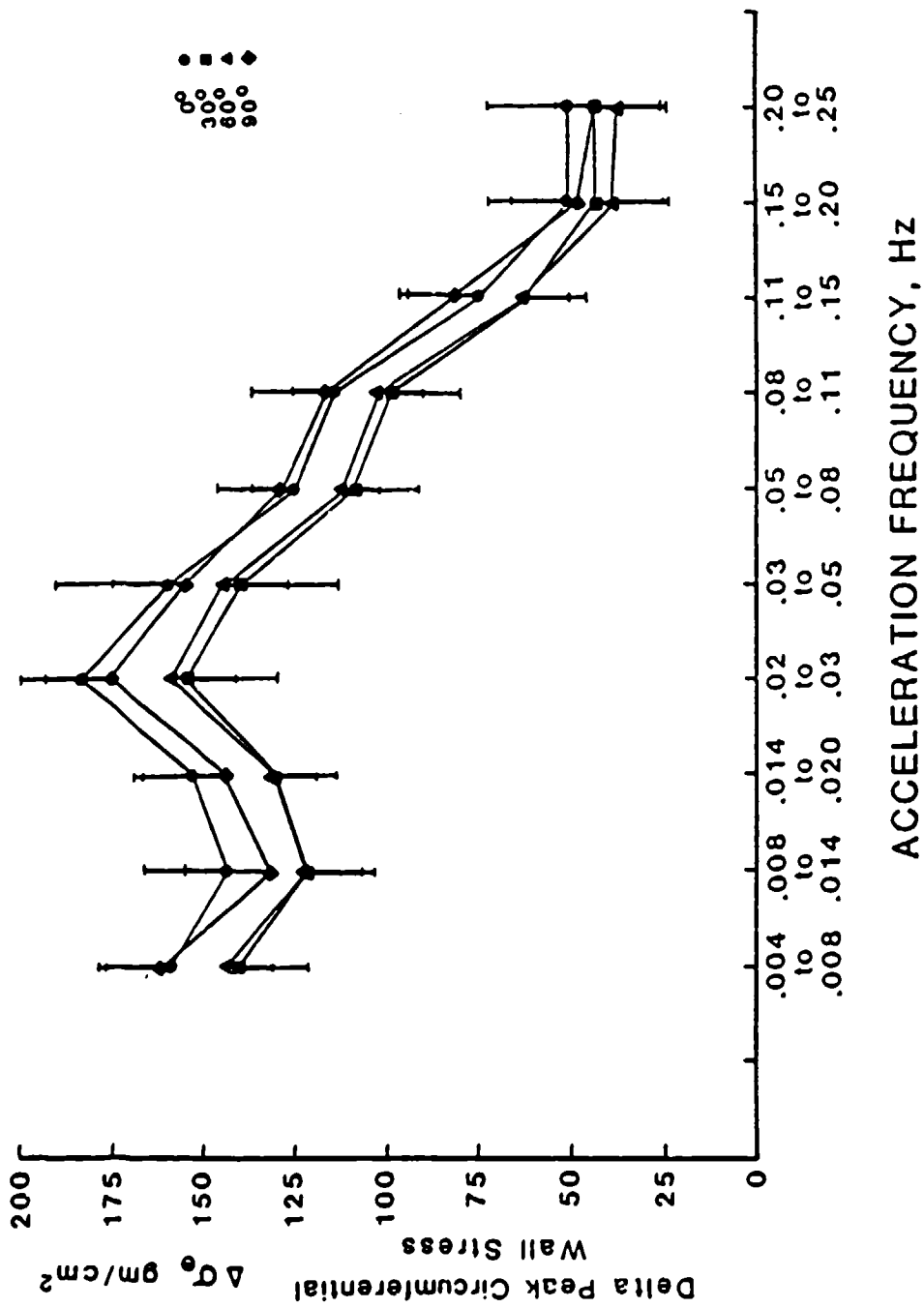


FIGURE 12
Delta (maximum - minimum) peak left ventricular circumferential wall stress (gm/cm²) versus acceleration frequency (Hz) in cardiac denervated animals.

variations in these variables. In contrast, there also appears to be a functional relationship in both groups of animals between acceleration-induced excursions in peak wall stress and acceleration-induced excursions in peripheral vascular resistance, although the acceleration-induced magnitudes of these parameters are not as well correlated. Thus, it appears that the dynamic peak wall stress response observed in the present study are related primarily to the magnitudes of aortic pressure and to the excursions of peripheral vascular resistance. These findings are consistent with those of other investigators (2) in that afterload (and consequently left ventricular wall stress) has long been known to be a function of the complex interrelations between aortic pressure and peripheral vascular resistance.

The behavior of the time relation angles for the normal group of animals (Figure 6) agree well with the first harmonic phase angles of mean aortic pressure in normal dogs exposed to the same acceleration stress reported by Marquis (16) and Charles (4). These investigators reported phase angles of the first Fourier component of mean aortic pressure to be constant across the acceleration frequency range for normal dogs, as was the case for the time relation angles for peak wall stresses in the present study. The aortic pressure responses in these studies were not strictly sinusoidal and thus the first Fourier phase angle is not totally indicative of the location of maximum and minimum aortic pressures with respect to the input acceleration. However, if second and higher harmonic amplitudes are small, as reported by Marquis (16), then the Fourier phase angle of these previous studies (when adjusted to a time relation angle) should be,

and are in the neighborhood of the high and low values in this study.

Marquis (16) also determined the first Fourier harmonic phase angle of effective systemic resistance in autonomically blocked dogs exposed to sinusoidal acceleration. He found that the phase angle in these blocked dogs increased (time relation angle decreased) by approximately 120° over the acceleration frequency range. This value compares favorably to the 133° difference from lowest to highest acceleration frequency found for the time relation angles in the cardiac denervated animals in the present study.

Knapp (13) also reported a similar finding for the time relation angle of total peripheral resistance in cardiac denervated versus normal dogs exposed to sinusoidal acceleration. He observed a steady decrease in the time relation angles for the cardiac denervated dogs for acceleration frequencies from 0.012 to 0.110 Hz (the highest acceleration frequency analyzed for angles) while the angle for the normal animals remained almost constant. The equivalent time relation angles for peripheral resistance reported by Marquis (16) and Knapp (13) agree well (slightly higher) with the time relation angles for maximum peak left ventricular wall stress for the present investigation.

It is evident from comparison of the aortic pressure and peripheral resistance phase angles investigations of Marquis (16), Knapp (13), and Charles (4), that the time relation angles for peak left ventricular wall stress in the cardiac denervated animals of the present study, are influenced, primarily by the time relation of peripheral vascular resistance to the input acceleration. In contrast, time relation angles observed for the normal animals in the present study appear to be governed principally by the time

relationship of aortic pressure. These are reasonable conclusions, in that one would expect, in cardiac denervated animals, similar time relations between peak wall stress and total peripheral resistance, since peripheral resistance is an indirect determinant of wall stress, and since the animal still has normal intact control over peripheral resistance. Likewise, in the normal animals, intact cardiac neural reflex mechanisms respond to control and regulate aortic pressure, resulting in qualitatively similar relationships in time relation angles for peak wall stress and aortic pressure.

Previous investigators have attributed the control and regulation of pressure and resistances for the high acceleration frequencies to non-neural hydraulic and intrinsic biomechanical mechanisms, implying that there is a complete lack of neural control of pressures and resistances at the higher acceleration frequencies. The results of the present study, however, indicate that neural mechanisms play at least a partial role in the response of peak wall stresses at the higher acceleration frequencies. Evidence for this observation is seen in the differences in time relation angles between the two groups of animals for acceleration frequencies above 0.03 Hz. This is not a contradictory finding, considering that one would expect cardiac mechanisms to be able to respond at frequencies even approaching 2 Hz, since the heart is called upon to change its pumping characteristics on a beat to beat basis (2).

CONCLUSIONS

The following conclusions were drawn from the results of the present investigation:

1. The use of the thin-walled prolate ellipsoidal model provided a reasonable estimate of the qualitative aspects of left ventricular wall stresses in normal and cardiac denervated canines exposed to sinusoidal acceleration when dimensions were obtained from ultrasonic measurement techniques.

2. Sinusoidal whole body spinal-axis acceleration ($\pm 2G$) in the 0.004 to 0.25 Hz frequency range was a suitable global noninvasive stimulus capable of producing significant changes in levels of left ventricular peak wall stress.

3. The largest acceleration-induced peak wall stress observed in this study occurred at the 0.02 to 0.03 Hz acceleration frequency range in both the normal and cardiac denervated animals. This largest stress occurred at 90° and in the circumferential direction for both groups.

4. The smallest acceleration-induced peak wall stress occurred for acceleration frequencies below 0.008 Hz in the normal animals and at acceleration frequencies below 0.014 Hz in the cardiac denervated animals. This smallest stress occurred at 30° and in the longitudinal direction for both groups.

5. For acceleration frequencies below 0.02 Hz, levels of maximum peak wall stress were significantly lower in the normal group than in the cardiac denervated group, implying regulation of stress levels by cardiac neural mechanisms.

6. For acceleration frequencies above 0.05 Hz, the time of occurrence of maximum and minimum peak wall stresses were significantly earlier within the acceleration cycle in the normal group than in the cardiac denervated group, implying neurally-mediated influences at the highest frequencies.

7. Evidence indicated that the magnitude and time of occurrence within the acceleration cycle of the maximum peak wall stress in the normal animals was closely associated to arterial pressure, while more closely related to peripheral resistance in the cardiac denervated animals.

8. Cardiac neural mechanisms played an important role in the determination of the time of occurrence within an acceleration cycle of the maximum and minimum peak wall stresses for acceleration frequencies above 0.05 Hz, while evidence in the literature indicates that neural reflex mechanisms probably do not play a significant role in the control and regulation of aortic pressure and peripheral resistance above acceleration frequencies of 0.05 Hz.

9. In order to more completely delineate the components of left ventricular wall stress, future research efforts in this area should attempt to describe the stress responses to acceleration inputs other than sinusoidal in normal and cardiac denervated preparations, as well as in preparations employing varying degrees of pharmacologic blockade.

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